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**CHIRAL PHOSPHINES, TRANSITION METAL COMPLEXES
THEREOF AND USES THEREOF IN ASYMMETRIC REACTIONS**

5 This application claims priority from Provisional Application Serial
Numbers 60/164,508 filed on November 10, 1999 and 60/187,851 filed on March
8, 2000.

BACKGROUND OF THE INVENTION

10

1. FIELD OF THE INVENTION

15 The present invention relates to novel chiral phosphines for applications in
asymmetric catalysis. More particularly, the present invention relates to transition
metal complexes of these chiral phosphine ligands. The transition metal
complexes according to the present invention are useful as catalysts in asymmetric
reactions.

2. DESCRIPTION OF THE PRIOR ART

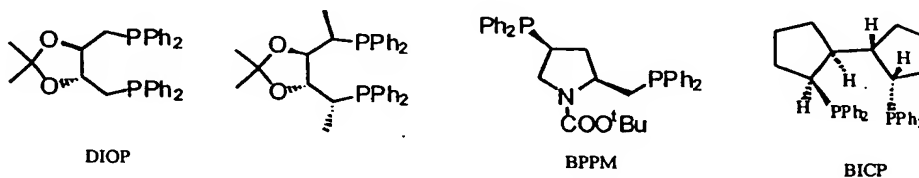
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Several families of conformationally rigid chiral bisphosphines suitable for
use in transition metal-catalyzed enantioselective transformations are known. The
present invention discloses asymmetric catalysts based on chiral bidentate
phosphines with multi-stereogenic centers in the backbone. Conformational
25 analysis leads to the result that one of the stereochemical arrangements of the
many diastereomers is the most enantioselective ligand for transition metal-
catalyzed asymmetric reactions. A common feature of these ligands is that
appropriate stereogenic centers in these ligands can restrict conformational
flexibility of the ligands and thus the efficiency of chiral transfer can be enhanced
30 through the ligand rigidity.

Molecular chirality plays a very important role in science and technology. The biological activities of many pharmaceuticals, fragrances, food additives and agrochemicals are often associated with their absolute molecular configuration.

While one enantiomer gives a desired biological function through interactions with natural binding sites, another enantiomer usually does not have the same function and sometime has deleterious side effects. During the last few decades, asymmetric catalysis has been developed as effective method for the production of enantiomerically pure compounds.

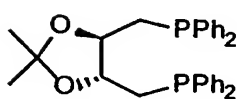
Development of chiral phosphine ligands has played a significant role in various types of transition metal-catalyzed asymmetric synthesis (H. Brunner, W. Zettlmeier, *Handbook of Enantioselective Catalysis with Transition Metal Compounds*, Vol. 2, Ligands-References, VCH Verlagsgesellschaft, weinheim, 1993, p359). Especially, chiral diphosphines of C_2 -symmetry are of special interest due to their high enantioselectivities in asymmetric reactions. Chiral 1,4-bisphosphines, such as, DIOP (H. B. Kagan, T.-P. Dang, *J. Am. Chem. Soc.* **1972**, *94*, 6429), BPPM (K. Achiwa, *J. Am. Chem. Soc.* **1976**, *98*, 8265; and I. Ojima, N. Yoda, *Tetrahedron Lett.* **1980**, *21*, 1051.), BICP (G. Zhu, P. Cao, Q. Jiang, X. Zhang, *J. Am. Chem. Soc.*, **1997**, *119*, 1799) have been developed for transition metal-catalyzed asymmetric catalysis.



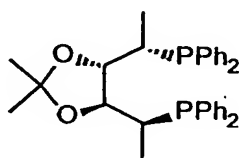
Chiral 1,4-bisphosphines

Although these ligands are effective for some asymmetric transformations, there are some areas in where these ligands are not efficient in their activity and selectivity. Thus, the design and synthesis of new chiral phosphine ligands that are effective in the more difficult asymmetric transformations remain important and challenging endeavors. The present invention discloses design and synthesis of novel chiral bisphosphines based on the conformational analysis.

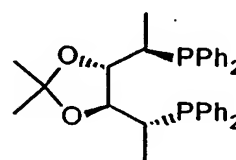
The relationship between catalyst conformation and product configuration has been studied before. In general, the observed high asymmetric induction is attributed to the well define formed chiral conformation of the chelate. Based on a number of experiments, enantioselectivity with DIOP is not high in many asymmetric reactions. A possible explanation for this observation might be that the chiral centers are too far and the seven-membered chelate ring of DIOP (1) bound to transition metal (e.g., rhodium) is too conformationally flexible (the transfer of backbone chirality to the phenyl groups on the phosphine goes through a methylene group).



1 (R,R)-Diop



2



3 (R,S,S,R)-Diop*

To overcome this drawback, Kagan synthesized ligand 2 in which there are two more chiral centers closer to the phosphorus atom (H. B. Kagan, J. C. Fiaud, C. Hoornaert, D. Meyer, J. C. Poulin, *Bull. Soc. Chim. Belg.* 1979, 88, 923).

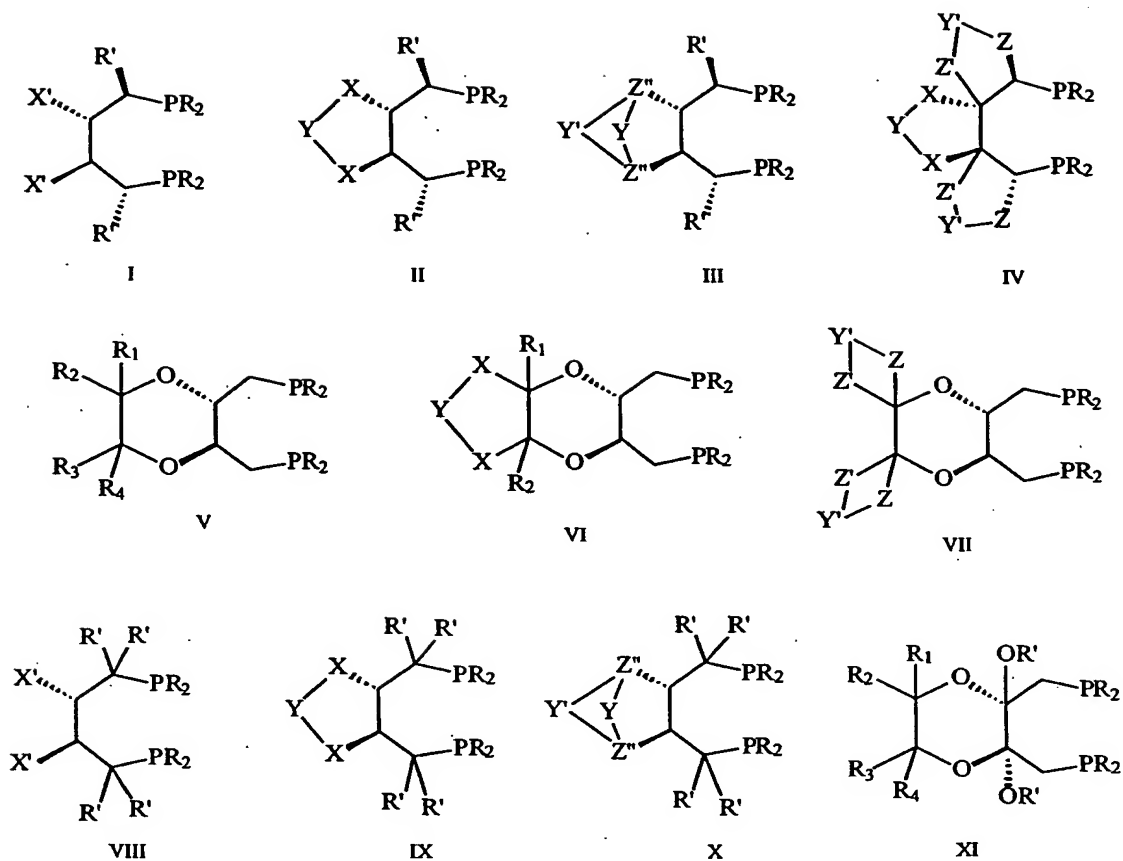
Unfortunately, in this case the enantioselectivity for asymmetric hydrogenation of dehydroaminoacid was substantially lower than in the case of DIOP. We reasoned that the poor selectivity may be caused by the two newly introduced methyl groups which may have an axial position in the seven-membered chelate ring influencing enantioselectivity (R. Selke, M. Ohff, a. Riepe, *Tetrahedron* 1996, 52, 15079).

This explanation suggests that the revised configuration of the two chiral centers in ligand 3 (R,S,S,R)-DIOP* (star) will force every substituent to have an equatorial position and form a well defined conformation chelated with Rh so that a high enantioselectivity can be achieved. We have found that bisphosphine 3 is a much more effective ligand than DIOP (1) and 2 for asymmetric hydrogenation reactions. This led to the conclusion that appropriate conformation of chiral ligands is the key to the high enantioselectivity, thereby providing a foundation on which the new chiral phosphines of the present invention are based.

Thus, while the hydrogenation of dehydroaminoacids (an electron-withdrawing alkene) with the Rh-based catalyst gave poor enantioselectivity {(a) Berens, U.; Leckel, D.; Oepen, S. C. *J. Org. Chem.* 1995, 60, 8204. (b) Berens, U.; Selke, R. *Tetrahedron: Asymmetry* 1996, 7, 2055}., we have achieved outstanding results for hydrogenation and simple enamides (an electron rich alkene) with 3 (R,S,S,R)-DIOP*.

SUMMARY OF INVENTION

The present invention includes a ligand selected from the group consisting of compounds represented by I through XI:



5

wherein X' is selected from the group consisting of: alkyl, aryl, substituted alkyl, substituted aryl, hydroxy, alkoxy, aryloxy, siloxy, thioalkoxy, arylthio, amino, alkylamino, dialkylamino, arylamino, diarylamino, alkylaryl amino, amido, ester, reverse ester, keto, halo, silyl and SH;

10

wherein R' is selected from the group consisting of: alkyl, aryl, substituted alkyl, substituted aryl, hydroxy, alkoxy, aryloxy, amino, alkylamino, dialkylamino, arylamino, diarylamino, alkylaryl amino and amido;

wherein each X, Z and Z' is independently selected from the group consisting of: O, NH, NR, CH₂, CHR, CR₂, C=O, S, SO₂, and SO;

wherein each Z" is independently selected from the group consisting of: N, P, CH, and CR;

5 wherein each R₁, R₂, R₃ and R₄ is independently selected from the group consisting of: H, alkyl, aryl, substituted alkyl, substituted aryl and OR;

wherein each Y and Y' is independently selected from the group consisting of: a diol protecting group residue, O, CO, C(OR)₂, CH(OR), CH₂, CHR, CR₂, CR₂, NR, SO₂, -(CH₂)_n- wherein n is 0 or an integer from 1 to 8,

10 -(CH₂)_nQ(CH₂)_m- wherein each n and m is independently an integer from 1 to 8, divalent phenyl, substituted divalent phenyl, 2,2'-divalent-1,1'-biphenyl, substituted 2,2'-divalent-1,1'-biphenyl, 2,2'-divalent-1,1'-binaphthyl, substituted 2,2'-divalent-1,1'-binaphthyl, 1,1'-ferrocene, substituted 1,1'-ferrocene, wherein the substituent in each of said substituted divalent phenyl, biphenyl, binaphthyl and ferrocene is one or more moiety each independently selected from the group
15 consisting of: alkyl, aryl, aralkyl, alkaryl, alkenyl, alkynyl, F, Cl, Br, I, OH, OR, SH, SR, COOH, COOR, SO₃H, SO₃R, PO₃H₂, PO₃HR, PO₃R₂, NH₂, NHR, NR₂, PR₂, AsR₂, SbR₂ and nitro; and

wherein each R is independently selected from the group consisting of:
20 alkyl, aryl, substituted alkyl, substituted aryl, fluoroalkyl, perfluoroalkyl and -CR'₂(CR'₂)_qQ(CR'₂)_pR' wherein each q and p is independently an integer from 1 to 8, Q is selected from the group consisting of: O, S, NR, PR, AsR, SbR, divalent aryl, divalent fused aryl, divalent 5-membered ring heterocycle and divalent fused heterocycle.

25

The present invention also includes a process for preparing a ligand enantiomer in high-enantiomeric purity. The process comprises the steps of:

contacting an enantiomer of tartaric acid diester and a diol protecting group in the presence of an acid catalyst to produce a bis-protected tartrate diester;

30 contacting said bis-protected tartrate diester and a reducing agent to convert the ester functional groups in said tartaric acid diester to a diol;

converting said diol to a sulfonate ester; and
displacing the sulfonate group in said sulfonate ester with lithium
diphenylphosphinide to produce the ligand enantiomer.

5 The present invention further includes a catalyst prepared by a process
comprising contacting a transition metal salt, or a complex thereof, and a ligand
selected from the group consisting of compounds represented by I through XI, as
described above.

10 The present invention still further includes a process for preparation of an
asymmetric compound using a catalyst according to the present invention. The
process comprises contacting a substrate capable of forming an asymmetric
product by an asymmetric reaction and a catalyst prepared by a process
comprising contacting a transition metal salt, or a complex thereof, and a ligand
15 selected from compounds represented by I through XI, as described above. The
transition metal complexes of the chiral ligands of the present invention produce
chiral products with an extremely high enantioselectivity. For example,
ruthenium complex of chiral (R,S,S,R)-DIOP* ligand reduces enamides with 99%
enantioselectivity to produce the corresponding amine in a 99% ee.

20

DETAILED DESCRIPTION OF INVENTION

25 The search for new efficient chiral ligands for practical asymmetric
catalytic reactions has not yet produced a universal ligand suitable for use in all
asymmetric reactions. For example, hydroformylation, requires relatively electron
deficient and flexible ligands for higher activity and selectivity, whereas other
reactions such as hydrogenation, requires relatively electron rich and more rigid
chiral ligands.

30 The ligand according to the present invention can be racemic, i.e., racemic
mixture of enantiomers, or a non-racemic mixture of enantiomers. Preferably, the

ligand according to the present invention is one of the enantiomers. When the ligand is a non-racemic mixture of enantiomers, preferably it has an optical purity of at least 85% ee, more preferably, it has an optical purity of at least 95% ee.

5 The various types of ligands of the present invention are described below.

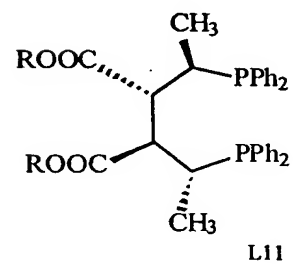
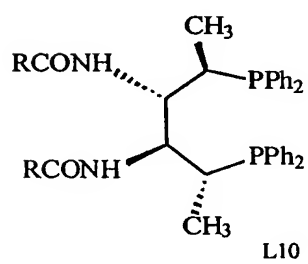
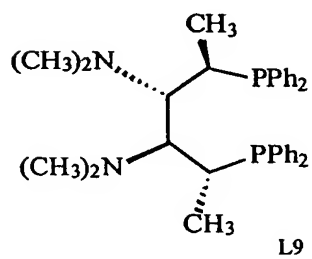
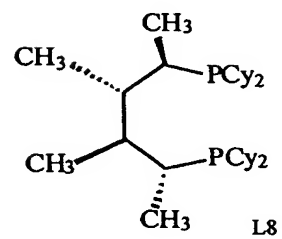
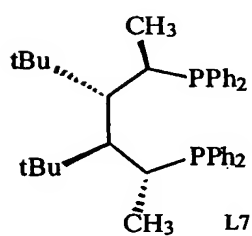
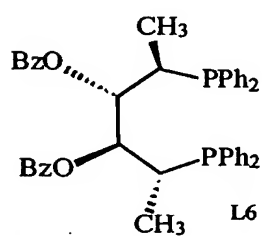
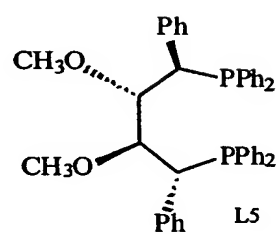
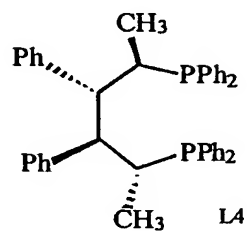
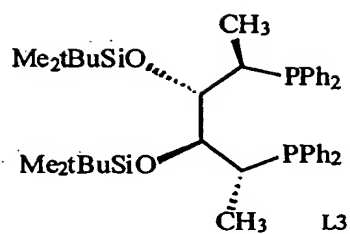
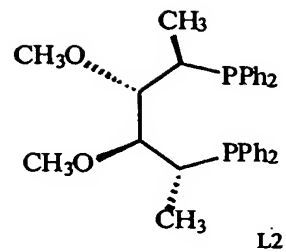
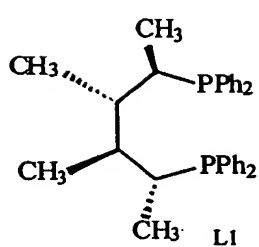
 The chiral ligands according to the present invention include 1,4-bisphosphines **I** to **XI**.

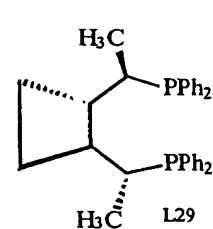
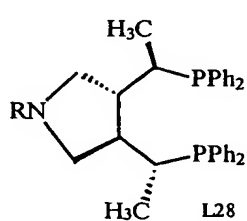
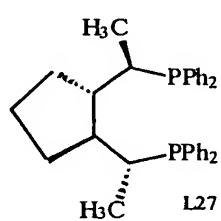
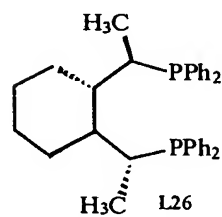
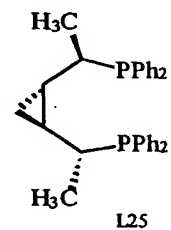
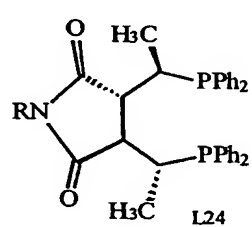
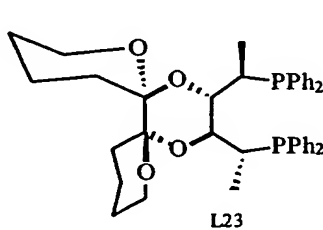
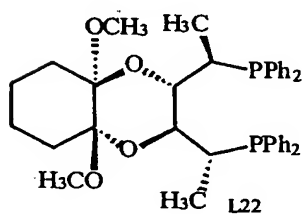
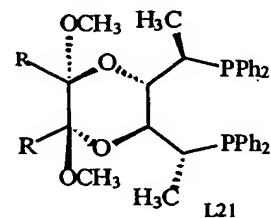
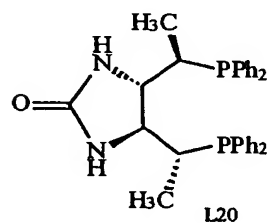
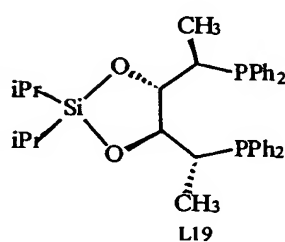
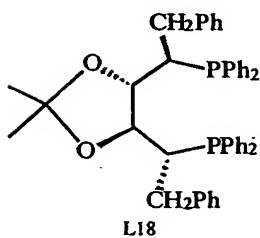
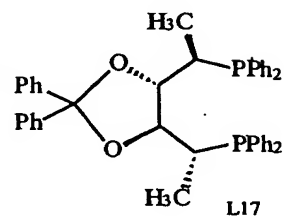
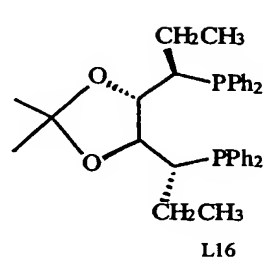
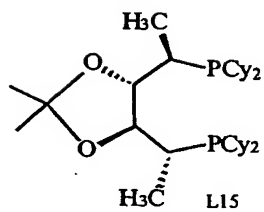
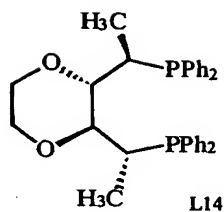
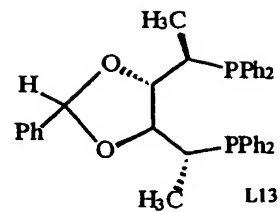
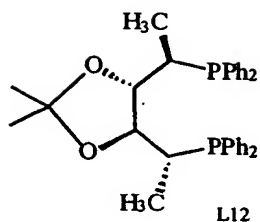
10 Ligands represented by formula **I** have four stereogenic centers in the backbones. Ligands represented by formula **II** have a ring structure connected with two middle stereogenic centers. Ligands represented by formula **III** have bicyclic structure in the middle of two stereogenic centers. Ligands represented by formula **IV** have three ring systems to control the conformation of the ligands.
15 Ligands represented by formula **V**, **VI** and **VII** have a six-membered ring in the DIOP. The conformation is controlled by the special class of protecting groups. Ligands represented by formula **VIII** have two stereogenic centers in the middle, which transfers the chirality through the adjacent quarternary carbons. Ligands represented by formula **IX** have a ring structure with two stereogenic centers in
20 the middle, which transfer the chirality through the adjacent quarternary carbons. Ligands represented by formula **X** have a bicyclic structure with two stereogenic centers in the center, which transfer the chirality through the adjacent quarternary carbons. Ligands represented by formula **XI** have a six-membered ring in the DIOP.

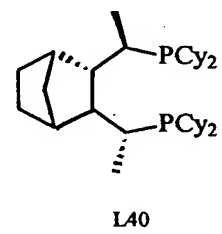
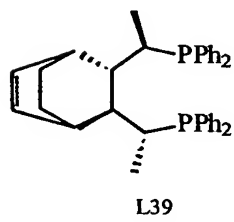
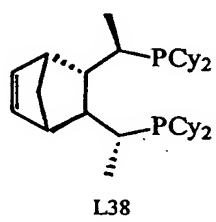
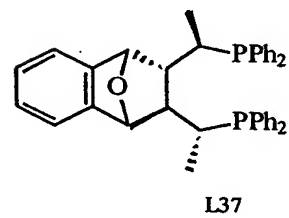
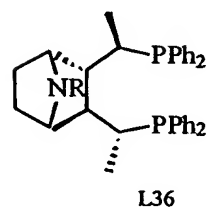
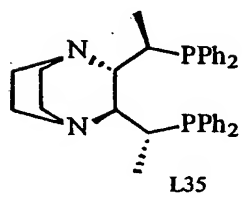
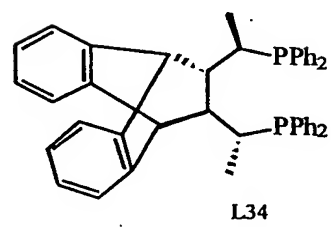
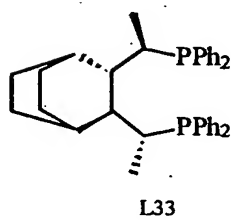
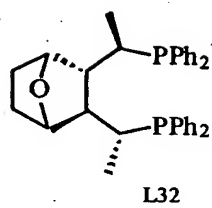
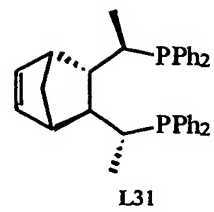
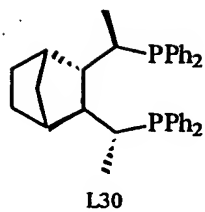
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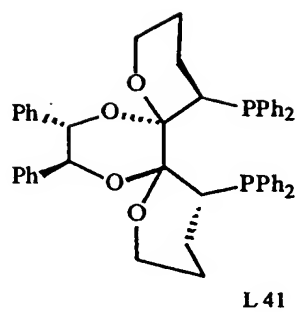
 In formula **IX**, R' can be hydrogen when X is an NH or an NR group.

 The preferred ligands of the present invention are selected from ligands represented by formulae **I** through **XI**, which include members represented by the
30 formula **L1** through **L102**, as depicted below:

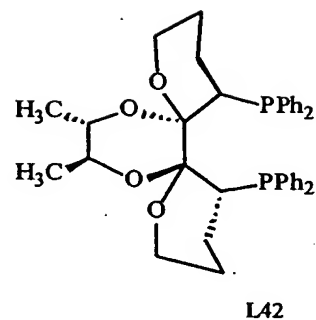




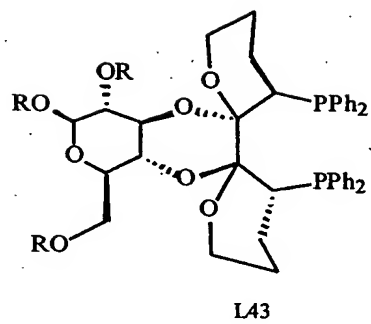




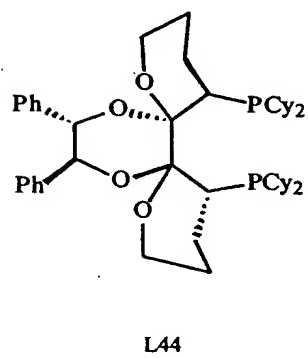
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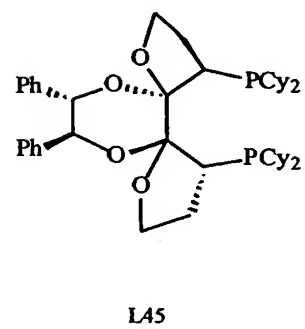
L42



L43

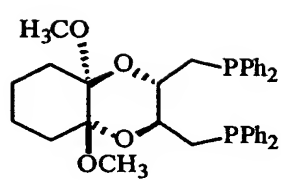


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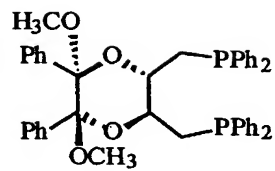


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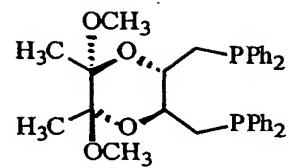
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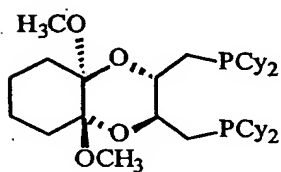
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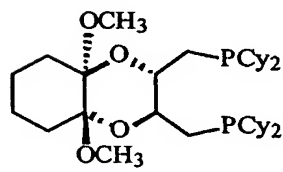
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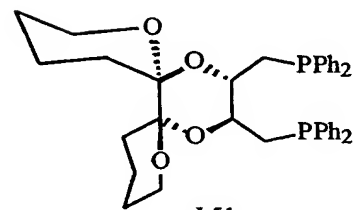
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L49



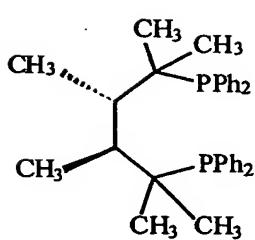
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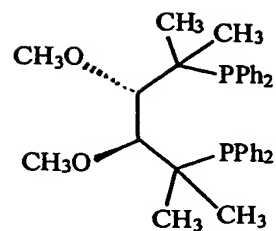
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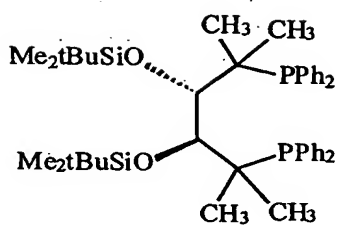
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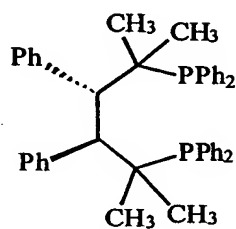
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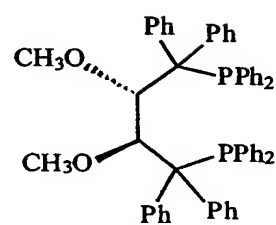
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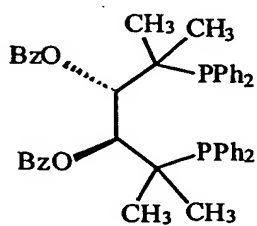
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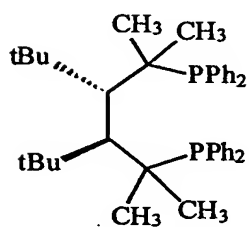
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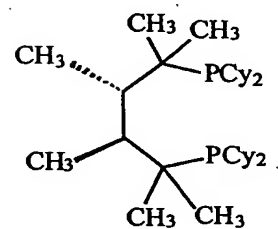
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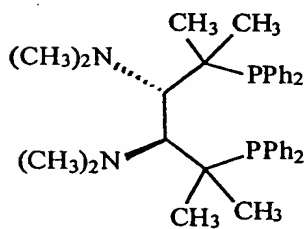
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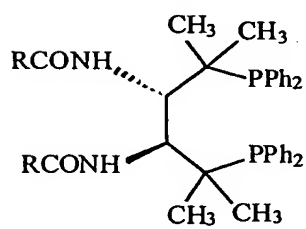
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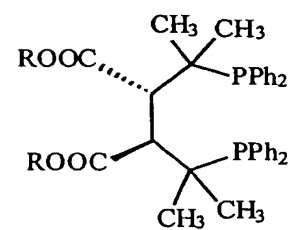
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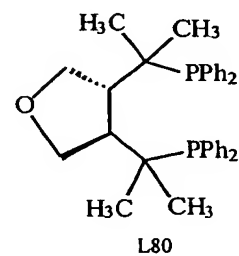
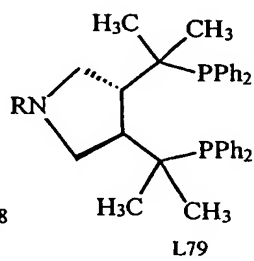
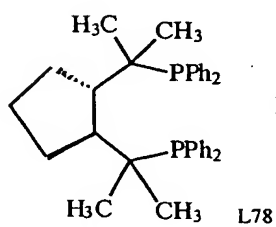
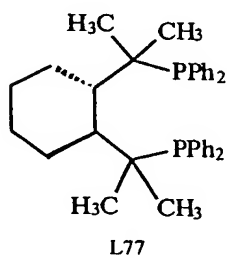
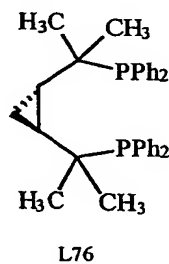
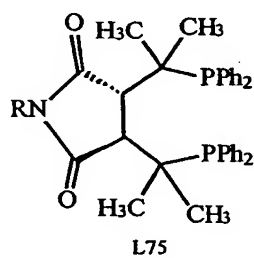
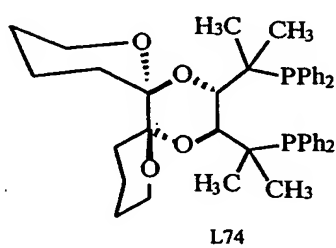
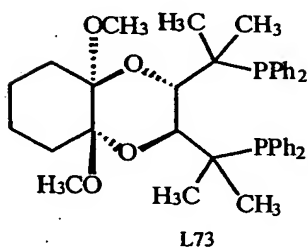
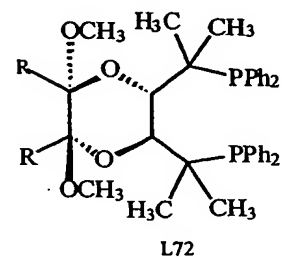
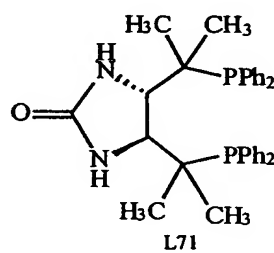
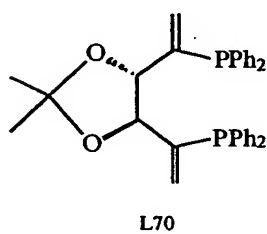
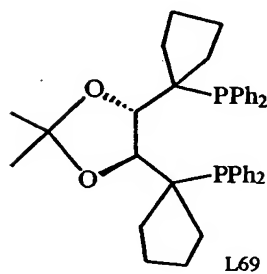
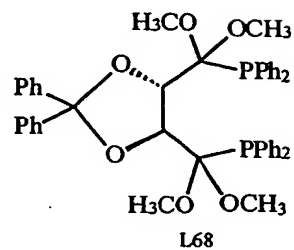
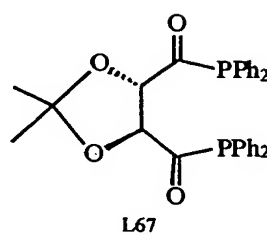
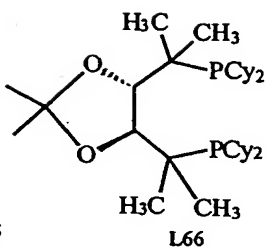
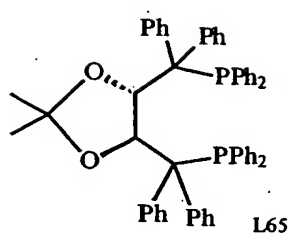
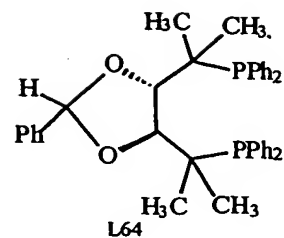
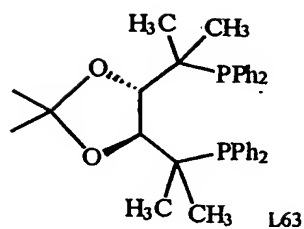
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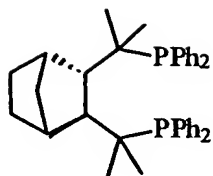


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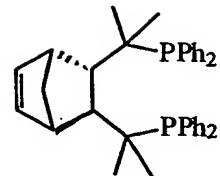


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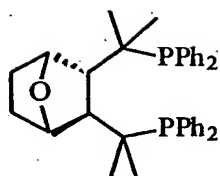




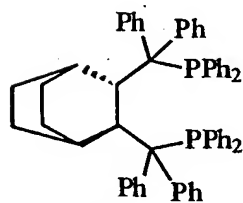
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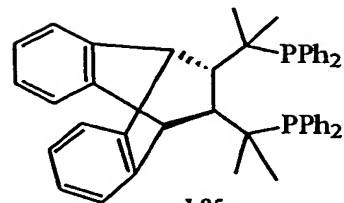
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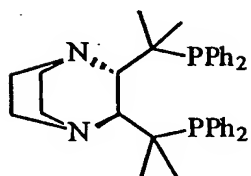
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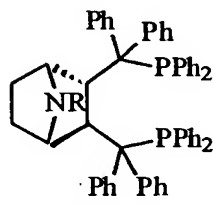
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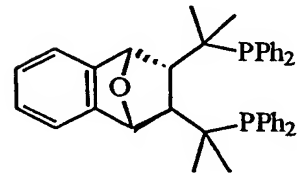
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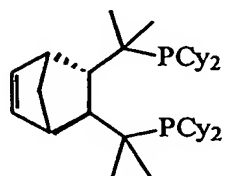
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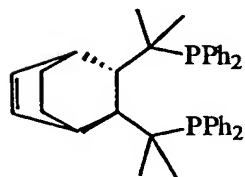
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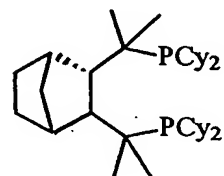
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The ligand of the present invention can be used in the monomeric form or in a polymeric or copolymeric form, either as a free ligand or as a ligand supported on a support material. Preferably, the support material is either a polymer support, such as, polystyrene, polyacrylate, resin, PEG, MeO-PEG, dendritic polyester or dendritic polyenamide, or the support material is an inorganic support, such as, silica, alumina, zeolite, molecular sieve or mesoporous material. The ligand may be attached to the support material through physical interactions or it can be linked to the support material by a linker group, such as, $\text{NH}(\text{CH}_2)_n\text{Si}(\text{OEt})_3$ wherein $n = 1$ to 8, $\text{CO}(\text{CH}_2)_n\text{Si}(\text{OEt})_3$, $(\text{CH}_2)_n\text{Si}(\text{OEt})_3$, C-O, C-N and NCF_2 linker. The ligand may be substituted by at least one water-soluble functional group, such as, sulfuric, phosphoric, carboxylic, quaternary ammonium and MeO-PEG groups.

Organic, inorganic and polymer-supported biphasic catalysts are also included. The chiral catalysts of the present invention are useful in a variety of transition metal-catalyzed asymmetric reactions.

As for the ligand, the catalyst according to the present invention can be racemic, such as, a racemic mixture of enantiomers, or it can be a non-racemic mixture of enantiomers. Preferably, the catalyst according to the present invention is one of the enantiomers. When the ligand according to the present invention is a non-racemic mixture of enantiomers, preferably it has an optical purity of at least 85% ee, more preferably, it has an optical purity of at least 95% ee.

Suitable transition metals for the preparation of the catalyst include Pt, Pd, Rh, Ru, Ir, Cu, Ni, Mo, Ti, V, Re and Mn.

The catalyst can be prepared by contacting a transition metal salt or its complex and a ligand selected from 1,4-bisphosphines I to XI. The transition metal salt or complex can be PtCl_2 ; $\text{Pd}_2(\text{DBA})_3$; $\text{Pd}(\text{OAc})_2$; $\text{PdCl}_2(\text{RCN})_2$; $(\text{Pd}(\text{allyl})\text{Cl})_2$; $(\text{Rh}(\text{COD})\text{Cl})_2$; $(\text{Rh}(\text{COD})_2)\text{X}$; $\text{Rh}(\text{acac})(\text{CO})_2$;

Rh(ethylene)₂(acac); Rh(CO)₂Cl₂; Ru(RCOO)₂(diphosphine);
 Ru(methylallyl)₂(diphosphine); Ru(aryl group)X₂(diphosphine); RuCl₂(COD);
 (Rh(COD)₂)X; RuX₂(diphosphine); RuCl₂(=CHR)(PR'₃)₂; Ru(ArH)Cl₂;
 Ru(COD)(methylallyl)₂; (Ir(COD)₂Cl)₂; (Ir(COD)₂)X; Cu(OTf); Cu(OTf)₂;
 5 Cu(Ar)X; CuX; NiX₂; Ni(COD)₂; MoO₂(acac)₂; Ti(OiPr)₄; VO(acac)₂; MeReO₃;
 MnX₂ or Mn(acac)₂; wherein each R and R' can independently be alkyl or aryl; Ar
 is an aryl group; and X is a counteranion. The preferred counteranions include
 halogen, BF₄, B(Ar)₄ wherein Ar is 3,5-di-trifluoromethyl-1-phenyl, ClO₄, SbF₆,
 CF₃SO₃, RCOO and a mixture thereof.

10

The catalyst may be prepared in situ or as an isolated compound. An
 example of the preferred catalyst of the present invention is chiral ruthenium
 complex with a ligand selected from 1,4-bisphosphines I to XI.

15

In another aspect, the present invention includes a process for preparation
 of an asymmetric compound using the catalysts described above. The process
 includes the step of contacting a substrate capable of forming an asymmetric
 product by an asymmetric reaction and a catalyst prepared by contacting a
 transition metal salt, or a complex thereof, and a 1,4-bisphosphine ligand
 20 represented by I to XI.

20

Suitable asymmetric reactions include hydrogenation, hydride transfer,
 hydrosilylation, hydroboration, hydrovinylation, hydroformylation,
 hydrocarboxylation, isomerization, allylic alkylation, cyclopropanation, Diels-
 25 Alder reaction, Heck reaction, isomerization, Aldol reaction, Michael addition and
 epoxidation.

25

Preferably, the asymmetric reaction is hydrogenation and the substrate to
 be hydrogenated is an ethylenically unsaturated compound, imine, ketone,
 30 enamine, enamide, and vinyl ester. Suitable catalysts for the hydrogenation of
 ketones to produce a chiral alcohol include chiral ruthenium complex with a

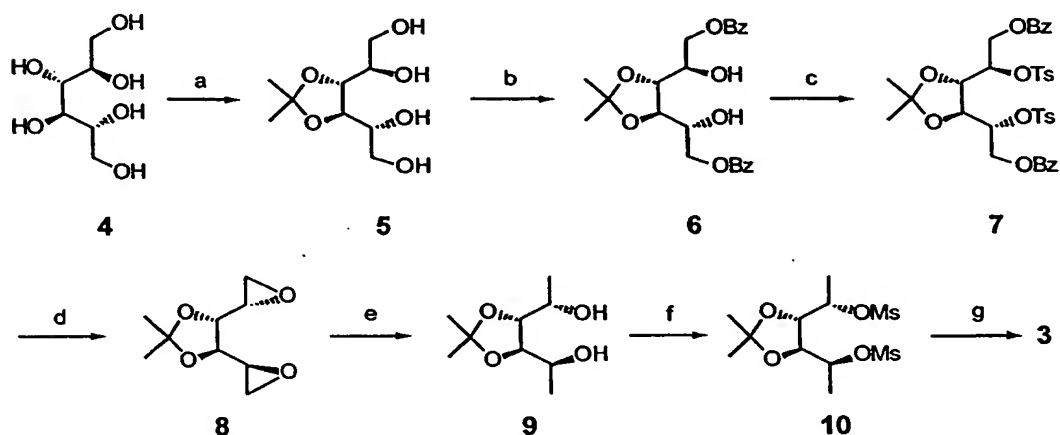
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ligand selected from 1,4-bisphosphines I to XI, particularly Ru complex of (R,S,S,R)-DIOP*.

Synthetic route to ligand (R,S,S,R)-DIOP* 3 is shown in Scheme below.

5

Scheme



a. (i) Acetone, H_2SO_4 ; 81%; (ii). AcOH , H_2O , 40°C , 2.5 h; 78%. b. BzCl , pyridine, CH_2Cl_2 , -78°C . c. TsCl , pyridine, DMAP, 0°C , 4 h. d. K_2CO_3 , CH_3OH , rt. 65% from 5. e. Et_3BH , THF, 0°C . 83% f. MsCl , Et_3N , CH_2Cl_2 , 0°C , 96% g. Ph_2PH , $n\text{-BuLi}$, THF, 0°C ~r.t., 67%.

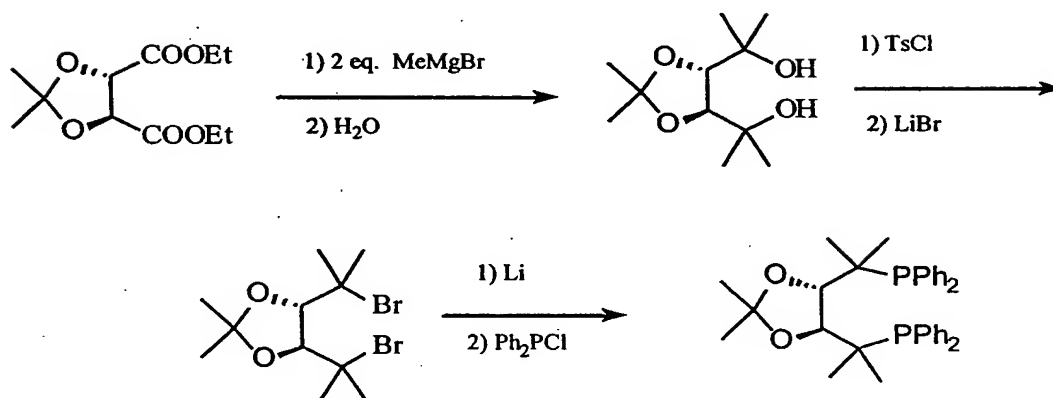
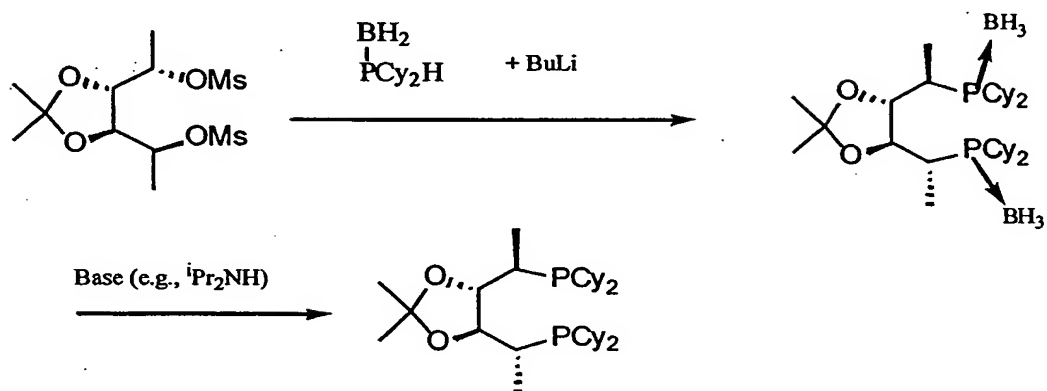
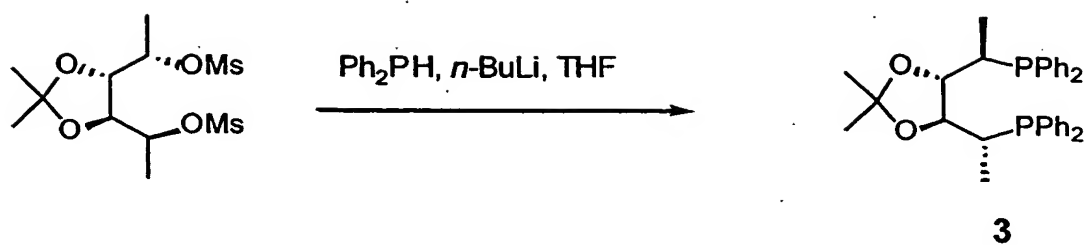
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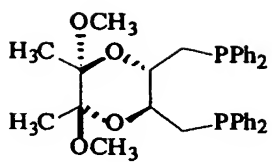
Commercially available *D*-mannitol 4 was also used as the starting material. *D*-mannitol 4 is first transformed into 3,4-*O*-isopropylidene-*D*-mannitol 5 which is dibenzoylated (5→6), ditosylated (6→7). Transesterification of the benzoate of 7 liberates primary alkoxides and the concomitant intramolecular $\text{S}_{\text{N}}2$ reaction occurs with inversion of configuration at C_2 and C_5 . Superhydride reduction of the diepoxide 8 afford the desired diol 9. Bismesylate 10 was obtained using normal basic medium conditions in high yield. Nucleophilic attack

15

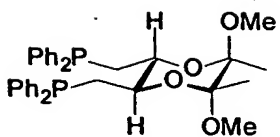
of **10** with diphenyl phosphine in the presence of *n*-BuLi produced **3** as a colorless oil in 67% yield. The advantages of this synthetic route come from the versatility of diepoxide **8**. Nucleophilic opening of the diepoxide **8** with various metal reagent (e.g., CH₃MgBr) leads to enantiomerically pure 1,4-diols with various kinds of R group instead of methyl group (P. Allevi, M. Anastasia, P. Ciuffreda, A. M. Sanvito, *Tetrahedron: Asymmetry* 1994, 5, 927). Furthermore, we can potentially to prepare the enantiomer of ligand **3** using the same starting material in principal. Protection of the 3,4-isopropylidene diol for ligand **2**, and then reversion of the configurations of C₃ and C₄ via a Mitsunobu reaction will provide the expected diol derivatives for the enantiomer of **3**.

The (R,S,S,R)-DIOP* ligand (**3**) was tested in the rhodium catalyzed asymmetric hydrogenation of enamide. The active catalyst employed in our study was generated in situ from a neutral Rh complex [Rh(COD)Cl]₂ or a cationic Rh complex [Rh(COD)₂]SbF₆, and **3** (R,S,S,R)-DIOP* (1:1.1). Enamide **11a** was chosen as a model substrate to screen various reaction conditions. The results were listed in Table 1 together with Kagan's results using DIOP (H. B. Kagan, N. Langlois, T. P. Dang, *J. Organomet. Chem.* 1975, 90, 353). Both of neutral and cationic Rh catalyst formed in situ with **3** (R,S,S,R)-DIOP* works well on this hydrogenation, while the cationic one is a little bit better. A small hydrogen pressure effect was found for this asymmetric catalytic system. Higher pressure give better reactivity and slightly decreasing in enantioselectivity. Strongly solvent effects on the enantioselectivity and reactivity were observed. With the changing of the solvent from polar methanol to CH₂Cl₂ and toluene, both of the selectivity and activity dropped down dramatically. It is reasonable to assume that the most stable chiral conformation containing **3** (R,S,S,R)-DIOP* is favorable in methanol. Overall, the optimal conditions use the catalyst generated in situ from [Rh(COD)Cl]₂ or [Rh(COD)₂]SbF₆ (2 mol%) and **3** (R,S,S,R)-DIOP* (2.2 mol%) and reaction is carried out at room temperature in methanol under 10 bar of H₂. Under similar reaction conditions, (+)-DIOP give only 51.6% ee with the R configuration.

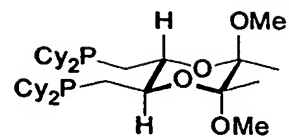




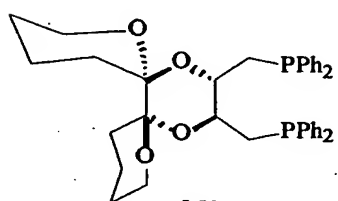
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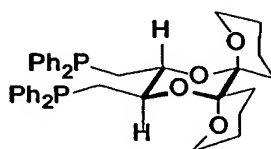
L48 (R, R, R, R)-T-Phos



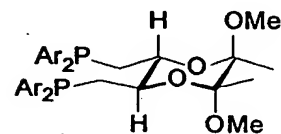
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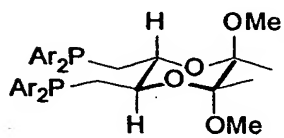
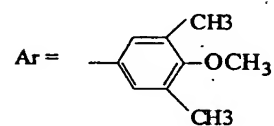
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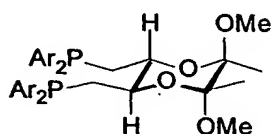
(R, R, R, R)-L51



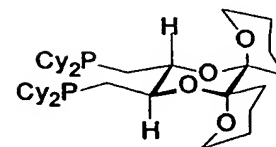
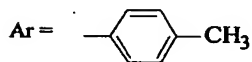
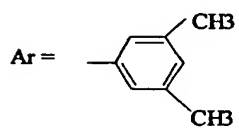
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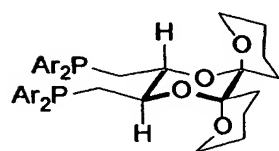
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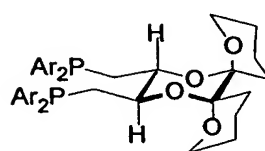
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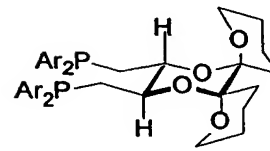
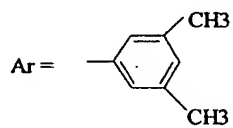
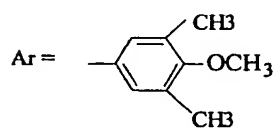
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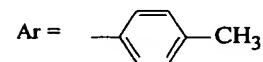
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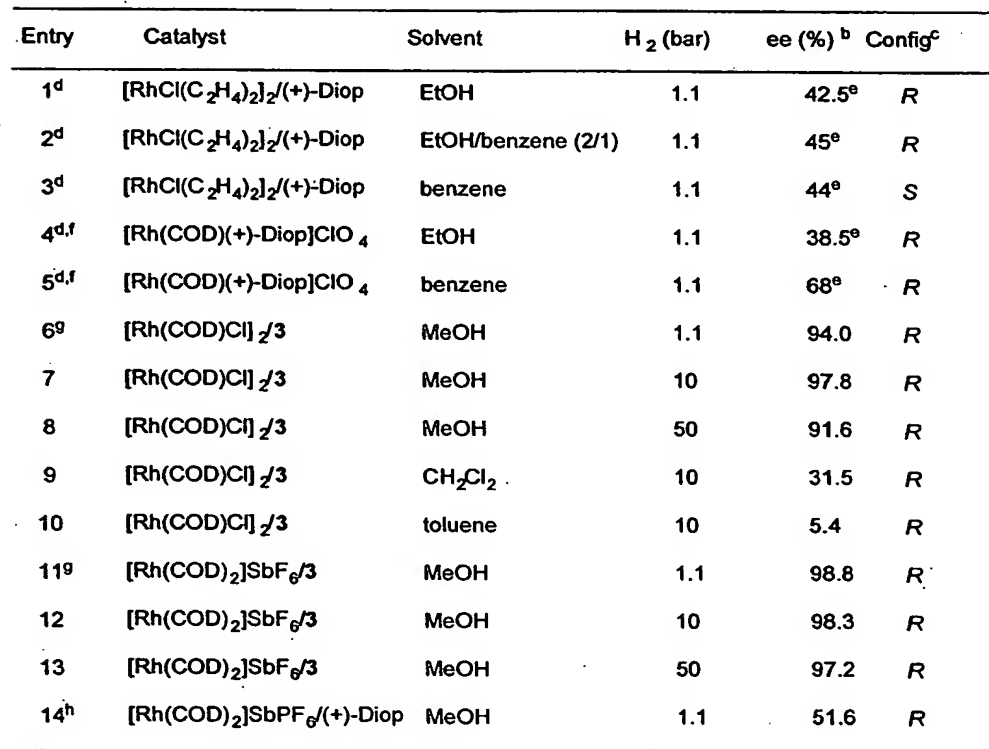
Accordingly, the present invention includes a process for preparing a ligand enantiomer in high enantiomeric purity. The process comprises the steps of:

- 5 contacting an enantiomer of tartaric acid diester and a diol protecting group in the presence of an acid catalyst to produce a bis-protected tartrate diester;
- contacting said bis-protected tartrate diester and a reducing agent to convert the ester functional groups in said tartaric acid diester to a diol;
- converting said diol to a sulfonate ester; and
- 10 displacing the sulfonate group in said sulfonate ester with lithium diphenylphosphinide to produce the ligand enantiomer.

The scope of the asymmetric hydrogenation reaction with different substrates is shown in Table 2. High selectivities (97 ~ >99%) have been
15 achieved for hydrogenation of a series of α -aryl enamides using the optimal reaction conditions. An important feature of the Rh-3 (R,S,S,R)-DIOP* catalyst was observed when we extended this hydrogenation reaction to an α -aryl enamide with β -methyl group (entry 11). The hydrogenation reaction was not sensitive to the geometry of the substrates, as an isomeric mixture of (*Z*)- and (*E*)- enamides
20 with a ratio of 1:2 in 97.3% ee under the standard reaction conditions.

Overall, β -substituted isomeric enamide mixtures and β -methyl substituted enamides with different substituent on the 1-aryl group can be reduced in high yield with high enantioselectivities (97 ~ >99%). The enantioselectivities
25 achieved in the Rh-3 (R,S,S,R)-DIOP* system are among the best results with those obtained with other systems.

..



^a The reaction was carried out at rt under suitable psi of H₂ for 60 h. The catalyst was made *in situ* by stirring a solution of Rh precursor and the bisphosphine ligand in solvent 3 mL {[substrate (0.25 mmol, 0.083 M) / [Rh] / L = 1 : 0.02 : 0.022]}. The reaction went with >99% conversion. Otherwise stated ^b. Enantiomeric excesses were determined by chiral GC using a Supelco Chiral Select 1000 (0.25 mm x 15 m) column. ^c The absolute configuration was assigned by comparison of optical rotation with reported data. ^d These results are from reference. ^e Optical purity. ^f Preformed catalyst was used. ^g. Entries 6 and 11 with 20%, 35% conversion based on GC, respectively. ^h With >99% conversion in 24 h.

Table 2. Asymmetric Hydrogenation of Enamide 11 by a Rhodium-3 Complex ^a

Entry	Ar	R	Rh	ee (%) ^b
1	C ₆ H ₅	H	[Rh(COD)Cl] ₂	97.8
2	C ₆ H ₅	H	[Rh(COD) ₂]SbPF ₆	98.3
3	<i>p</i> -CF ₃ C ₆ H ₄	H	[Rh(COD)Cl] ₂	97.6
4	<i>p</i> -CF ₃ C ₆ H ₄	H	[Rh(COD) ₂]SbPF ₆	97.7
5	<i>m</i> -CH ₃ C ₆ H ₄	H	[Rh(COD)Cl] ₂	98.5
6	<i>m</i> -CH ₃ C ₆ H ₄	H	[Rh(COD) ₂]SbPF ₆	98.8
7	<i>p</i> -PhC ₆ H ₄	H	[Rh(COD)Cl] ₂	>99 ^c
8	<i>p</i> -PhC ₆ H ₄	H	[Rh(COD) ₂]SbPF ₆	>99 ^c
9	2-naphthyl	H	[Rh(COD)Cl] ₂	>99 ^c
10	2-naphthyl	H	[Rh(COD) ₂]SbPF ₆	99.0 ^c
11	C ₆ H ₅	CH ₃	[Rh(COD) ₂]SbPF ₆	97.3
12	C ₆ H ₅	<i>i</i> -propyl	[Rh(COD) ₂]SbPF ₆	99.0
13	C ₆ H ₅	Bn	[Rh(COD) ₂]SbPF ₆	98.6 ^c
14	<i>p</i> -CF ₃ C ₆ H ₄	CH ₃	[Rh(COD) ₂]SbPF ₆	98.3
15 ^d	<i>p</i> -MeOC ₆ H ₄	CH ₃	[Rh(COD) ₂]SbPF ₆	98.0 ^c
16	2-naphthyl	CH ₃	[Rh(COD) ₂]SbPF ₆	>99 ^c

^a The reaction was carried out at rt under 10 bar of H₂ for 48–60 h. The catalyst was made *in situ* by stirring a solution of Rh precursor and the bisphosphine ligand 3 in methanol 3 mL {[substrate (0.25 mmol, 0.083 M) / [Rh] / L = 1 : 0.02 : 0.022]}. The reaction went with >99% conversion. Otherwise stated ^b. Enantiomeric excesses were determined by chiral GC using a Supelco Chiral Select 1000 (0.25 mm x 15 m) column. The *R* absolute configuration was assigned by comparison of optical rotation with reported data. ^c Enantiomeric excesses were determined by chiral HPLC using a (S,S)-whelk-o1 column. ^d With 20% conversion based on the GC analysis.

Experimental

General Methods

All reactions and manipulations were performed in a nitrogen-filled glovebox or using standard Schlenk techniques. All reagents were obtained from Aldrich or Strem and used directly. Toluene, tetrahydrofuran (THF) and hexanes were distilled from sodium benzophenone ketyl under nitrogen. Methylene chloride (CH_2Cl_2) was distilled from CaH_2 . Methanol (CH_3OH) was distilled from Mg under nitrogen. Gas chromatography was carried out on Hewlett-Packard 6890 gas chromatographs using a Chiral Select 1000 column (Dimensions: 15 m \times 0.25 mm), carrier gas: He (1 mL/min⁻¹). HPLC analysis was carried out on a WatersTM 600 chromatograph with an (*S,S*)-Whelk-01 column from Regis Technologies, Inc. {particle size: 5.0 μm . column dimensions: 25 cm (length) \times 0.46 cm (i.d.)}. ¹H, ¹³C and ³¹P NMR were recorded on Bruker WM 360 spectrometers. Chemical shifts were reported in ppm downfield from tetramethylsilane with the solvent resonance as the internal stand or 85% H_3PO_4 as the external standard respectively. Optical rotation was obtained on a Perkin Elmer 241 polarimeter.

Synthesis of 3,4-*O*-isopropylidene-(3*S*,4*S*)-dihydroxy-(2*S*,5*S*)-hexandiol bis(methanesulfonate) 10

To a solution of 3,4-*O*-isopropylidene-(3*S*,4*S*)-dihydroxy-(2*S*,5*S*)-hexandiol (2.2g, 11.6 mmol) and triethylamine (4.9 mL, 34.8 mmol) in CH_2Cl_2 (30 mL) was added dropwise a solution of methanesulfonyl chloride (2.0 mL, 25.8 mmol) in CH_2Cl_2 (10 mL) at 0°C. After 30 min at 0°C, the reaction mixture was stirred for additional 30 min at rt, then quenched by saturated aqueous ammonium chloride solution (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3 \times 30 mL) and the combined organic solution was dried over Na_2SO_4 . After evaporation of the solvent, the residue was purified by a flash chromatography on silica gel eluted with CH_2Cl_2 /ethyl ether (9/1) to give a colorless oil 3.85 g in 96% yield. ¹H NMR (CDCl_3 , 360 MHz) δ = 4.82-4.76 (m, 2H), 3.99-3.96 (m, 2H), 3.03 (s, 6H), 1.45 (d, J = 6.6, 6Hz), 1.37 (s, 6H); ¹³C NMR (CDCl_3 , 90.56 MHz) δ =

110.14, 78.19, 76.26, 38.53, 26.75, 17.63. HRMS calcd for $C_{11}H_{23}O_8S_2$ (MH^+) 347.0834 and $C_{11}H_{22}O_8S_2Na$ (MNa^+) 369.0654; found: 347.0834 and 369.0654.

Synthesis of 3,4-O-isopropylidene-(3S,4S)-dihydroxy-(2R,5R)-

5 bis(diphenylphosphino)hexane 3 {(R,S,S,R)-DIOP*}

To a solution of diphenylphosphine (1.15 mL, 6.6 mmol) in THF (50 mL) was added *n*-BuLi in hexane (4.0 mL, 6.4 mmol) at -78°C over 5 min via a syringe. The resulting orange solution was warmed to rt and stirred for 1 hr. After cooling the mixture to -78°C , 3,4-O-isopropylidene-(3S,4S)-dihydroxy-(2S,5S)-
 10 hexandiol bis(methanesulfonate) 10 (1.04 g, 3.0 mmol) in THF (20 mL) was added over 20 min. The resulting orange solution was warmed to rt and stirred overnight. The white suspension solution was hydrolyzed with saturated aqueous NH_4Cl solution. The aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL) and the combined organic solution was dried over anhydrous Na_2SO_4 . After removal
 15 of the solvents under reduced pressure, the residue was purified by a flash chromatography on silical gel eluted with hexanes/ethyl acetate (95/5) to give a colorless oil 1.06 g in 67% yield. 1H NMR ($CDCl_3$, 360 MHz) δ = 7.56-7.52 (m, 8H), 7.38-7.33 (m, 12H), 3.78-3.76 (m, 2H), 2.50-2.46 (m, 2H), 1.14 (s, 6H), 0.91 (d, J = 7.0 Hz, 3H), 0.87 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 90.56 MHz) δ =
 20 136.7 (d, J = 14.8 Hz), 136.2 (d, J = 14.3 Hz), 133.8 (d, J = 8.5 Hz), 133.6 (d, J = 7.8 Hz), 128.9 (d, J = 1.9 Hz), 128.3 (d, J = 7.2 Hz), 108.0, 31.6 (d, J = 13.3 Hz), 27.4, 11.1, 11.0. ^{31}P NMR ($CDCl_3$) δ = -6.3 ppm.

General Procedure for Asymmetric Hydrogenation

25 To a solution of Rhodium precursor (0.005 mmol) in methanol (3 mL) in a glovebox was added bisphosphine (0.055 mL of 0.1 M solution in toluene, 0.0055 mmol). After stirring the mixture for 10 min, the enamide (0.25 mmol) was added. The hydrogenation was performed at rt under 1.1 ~ 50 bar of hydrogen for 24 ~ 60 h. After the hydrogen was released, the reaction mixture
 30 was passed through a short silica gel column to remove the catalyst. The enantiomeric excess was measured by capillary GC or HPLC directly without any

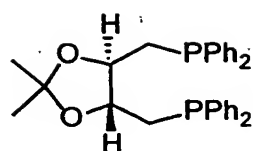
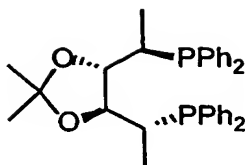
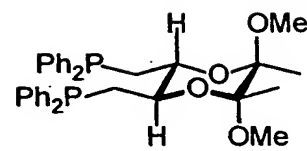
further purification. The absolute configuration of the products was determined by comparing the observed rotation with the reported value.

Asymmetric Rh-catalyzed Hydrogenation of Enamides with a 1,4-Diphenylphosphine Bearing Butane Diacetal Backbone

Considerable success has been achieved in the use of chiral arylphosphine ligands in Rh-catalyzed asymmetric hydrogenation reactions in the past three decades since the report of Kagan's DIOP **1**, the first chiral diphosphine for Wilkinson type catalysts. Although a lot of analogous of DIOP have been described, few of the modified DIOP produced superior results in the transition metal catalyzed reactions. We recently designed a derivative **3** of DIOP based on the chelate conformational analysis. The Rh complex of ligand **3** (*R, S, S, R*)-DIOP* afforded the best results in the enantioselective hydrogenation of β -substituted and β -unsubstituted enamides caused by the equatorial orientation of all substituents in the seven membered chelate ring. These results suggest that ligand **13** in which there is a deposited 1,4-dioxane six membered ring may form a more stable conformation when chelated with rhodium than DIOP **1**, and may induce higher enantioselectivities for some matched substrates. The highest selectivities in hydrogenation of enamides obtained with **2** (*R, S, S, R*)-DIOP*. Accordingly, the selectivity of bisphosphine ligand **13** was investigated in the hydrogenation of enamides and the results were compared with those obtained with DIOP **1**.

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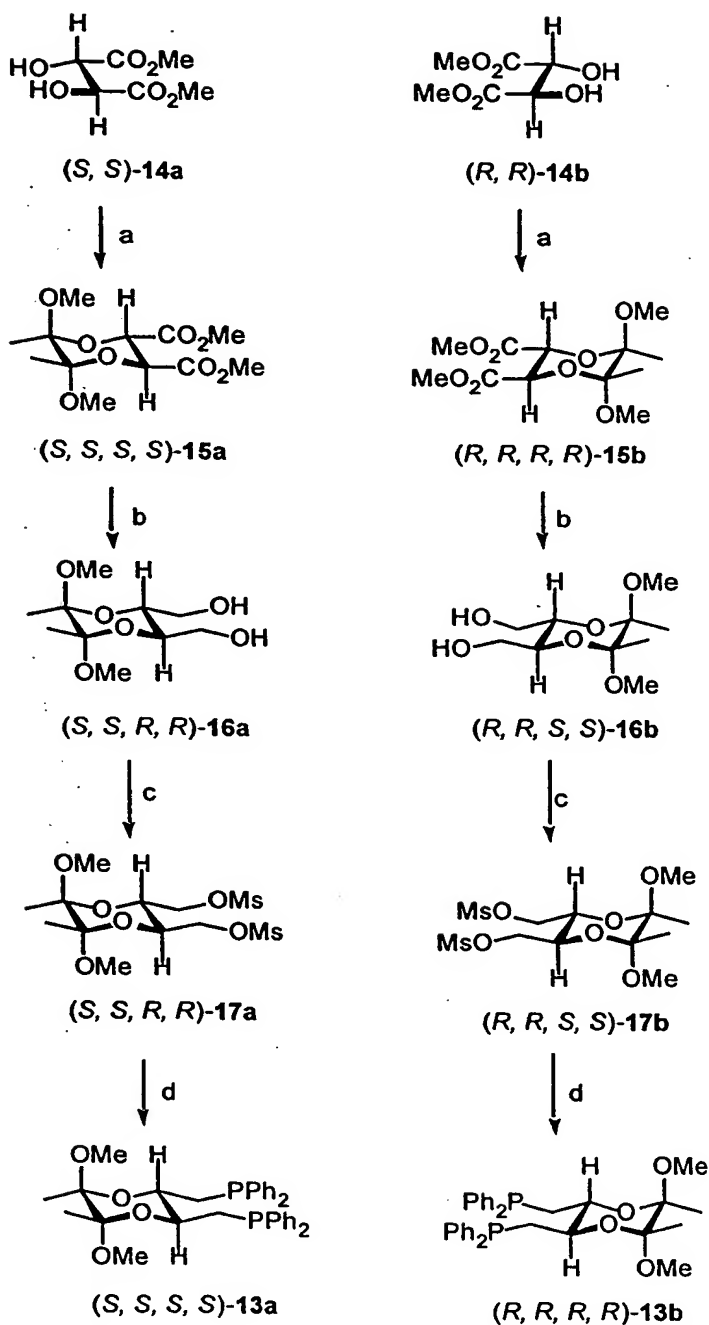
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**1** (*R, R*)-DIOP**3** (*R,S,S,R*)-DIOP***13b** (*R, R, R, R*)-T-Phos

5

The (*2R, 3R, 5R, 6R*)-5,6-bis[(diphenylphosphanyl)methyl]-2,3-dimethoxy-2,3-dimethyl[1,4]dioxane **13b** (named as T-Phos). The protected derivative **15b** was formed using acetal exchange in moderate yield, while the ditosylate of diol **16b** with only 53-76% yield that probably is caused by an intramolecular reaction with formation of a tetrahydrofurane derivative (Berens, U.; Leckel, D.; Oepen, S. C. *J. Org. Chem.* **1995**, *60*, 8204).

We found an efficient way to make **13b** using Ley's one-pot methodology of tartrate ester **14b**, 2,3-butanedione, trimethyl orthoformate, as well as catalytic amount of CSA (camphorsulfonic acid) as indicated in the Scheme below, to make the acetal **15b**. The advantage of this approach is that only one stereoisomer was formed and isolated in high yield very easily. We synthesized the bismesylate **17b** in 97% yield instead of making bistosylate. Nucleophilic attack produced the desired bisphosphine **13b** smoothly in 76% yield. The other enantiomer (*S, S, S, S*)-**13a** was also made in 73% yield via the same way from D-tartrate **14a**, as seen in the Scheme below.

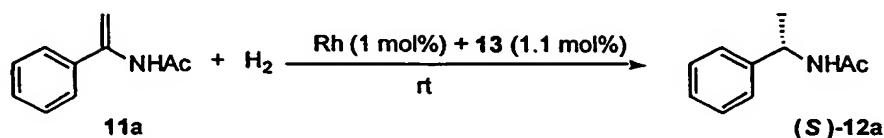


Scheme . Reagents and conditions: a) CH₃COCOCH₃ (1.2 equiv.), CSA (0.1 equiv.), CH(OCH₃)₃ (3.0 equiv.), CH₃OH, reflux, 14 h; b) LiAlH₄ (1.1 equiv.), THF, 0°C to RT, 0.5 h; c) MsCl, Et₃N, CH₂Cl₂, 0°C to RT, 2 h; d) Ph₂PH, BuLi, THF, 0°C to RT, 12 h.

The active catalyst rhodium complex was formed *in situ* by mixing 1.1 equivalent **3** and $[\text{Rh}(\text{COD})_2]\text{SbF}_6$ or $[\text{Rh}(\text{COD})\text{Cl}]_2$ and used directly. The asymmetric hydrogenation of enamides was explored initially varying different solvent and pressure of dihydrogen to screen optimal conditions for hydrogenation of *N*-acetylphenylethenamine **11a**. The cationic Rh complex $[\text{Rh}(\text{COD})_2]\text{SbF}_6$ was found to be more effective in the selectivity than a neutral precursor $[\text{Rh}(\text{COD})\text{Cl}]_2$ (Table 3, entry 2, 93.0% ee vs entry 1, 89.6% ee). As shown in Table 3, compared with methanol, toluene afforded a comparable enantioselectivity (entry 2, 93.0% ee vs entry 4, 93.9% ee), while the enantioselectivities dropped down to 87.3% ee in methylene chloride (entry 3) and 81.9% ee in THF (entry 5) respectively. Decreasing the pressure of H_2 from 75 psi to 25 psi resulted in a little bit increase of the enantioselectivity from 93.9 to 94.5% ee (entry 6). When **13a** (*S, S, S, S*)-T-Phos was used as the ligand, *N*-acetylphenylethenamine **11a** was hydrogenated smoothly in 93.1% ee with reversed configuration.

It is of interest to note that the diphosphine **13b** (*R, R, R, R*)-T-Phos resembled the ligand **1** (*R, R*)-DIOP, but led to an excess of the (*S*)-product. That is an unexpected enantioselectivity in comparison with the result for catalysts derivated from **1** (*R, R*)-DIOP having the analogous configuration as **13b** but leading to (*R*)-product.

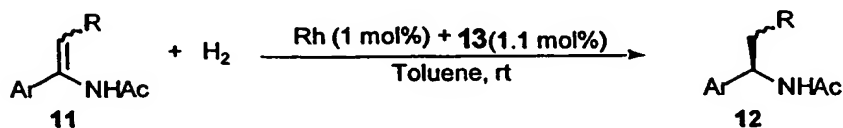
Several β -unsubstituted enamides were also hydrogenated with the Rh-**13b** T-Phos catalyst (Table 4, entries 3-6) and reduced to give the enantiomerically enriched α -arylethylamine derivatives with good enantioselectivities. The substrate **11b** with electron-withdrawing group (F_3C) gave a lower ee (entry 3, 82.8% ee) with the same configuration, but the electron donating substrates gave similar results as those of enamide **11a**.

Table 3. Asymmetric Hydrogenation of Enamides by a Rhodium-bisphosphine Complex ^a

Entry H	Ligand	Solvent	₂ (psi)	ee (%) ^b	Config ^c
1 ^d	13b	MeOH	75	89.6	S
2	13b	MeOH	75	93.0	S
3	13b	CH ₂ Cl ₂	75	87.3	S
4	13b	toluene	75	93.9	S
5	13b	THF	75	81.9	S
6	13b	toluene	25	94.5	S
7	13a	toluene	25	93.1	R

^a. The reaction was carried out at rt under suitable psi of H₂ for 24 h. The catalyst was made *in situ* by stirring a solution of Rh(COD)₂SbF₆ precursor and the bisphosphine ligand in solvent 4 mL {[substrate (0.5 mmol, 0.125 M) / [Rh] / 3 = 1 : 0.01 : 0.011]}. The reaction went with >99% conversion. Otherwise stated

^b. Enantiomeric excesses were determined by chiral GC using a Supelco Chiral Select 1000 (0.25 mm x 15 m) column. ^c. The absolute configuration was assigned by comparison of optical rotation with reported data. ^d. [Rh(COD)Cl]₂ was used as the precursor.

Table 4. Asymmetric Hydrogenation of Enamide **11** by Rhodium-**13** Complex^a

Entry (%)	Substrate	Ar	R	Ligand	ee ^b	Config. ^c
1	11a	C ₆ H ₅	H	13a	93.1	R
2	11a	C ₆ H ₅	H	13b	94.5	S
3	11b	<i>p</i> -CF ₃ C ₆ H ₄	H	13b	82.8	S
4	11c	<i>m</i> -CH ₃ C ₆ H ₄	H	13b	95.0	S
5	11d	<i>p</i> -PhC ₆ H ₄	H	13b	94.2 ^d	S
6	11e	2-naphthyl	H	13b	93.0 ^d	S
7	11f	C ₆ H ₅	CH ₃	13a	97.2	R
8	11f	C ₆ H ₅	CH ₃	13b	98.2	S
9	11g	C ₆ H ₅	<i>i</i> -propyl	13a	97.1	R
10	11g	C ₆ H ₅	<i>i</i> -propyl	13b	97.8	S
11	11h	C ₆ H ₅	Bn	13a	98.2 ^d	R
12	11h	C ₆ H ₅	Bn	13b	98.0 ^d	S
13	11i	<i>p</i> -CF ₃ C ₆ H ₄	CH ₃	13a	93.4	R
14	11i	<i>p</i> -CF ₃ C ₆ H ₄	CH ₃	13b	94.2	S
15	11j	<i>p</i> -MeOC ₆ H ₄	CH ₃	13a	98.3 ^d	R
16	11j	<i>p</i> -MeOC ₆ H ₄	CH ₃	13b	98.4 ^d	S
17	11k	2-naphthyl	CH ₃	13a	97.2 ^d	R
18	11k	2-naphthyl	CH ₃	13b	97.2 ^d	S

^a The reaction was carried out at rt under 25 psi of H₂ for 24 h. The catalyst was made *in situ* by stirring solution of Rh(COD)₂SbF₆ and the bisphosphine ligand **3** in toluene 4 mL ([substrate (0.5 mmol, 0.125) / [Rh] / **13** = 1 : 0.01 : 0.011]). The reaction went with >99% conversion. Otherwise stated ^b. nantiomer excesses were determined by chiral GC using a Supelco Chiral Select 1000 (0.25 mm x 15) column. ^c. The absolute configuration was assigned by comparison of optical rotation with reported data. ^d. Enantiomer excesses were determined by chiral HPLC using a (S,S)-Whelk-O1 column.

Exciting results were obtained in the hydrogenation of an α -aryl enamide with a β -methyl group. Generally, the catalyst system can hydrogenate such β -substituted enamide (Table 4, entries 7-18) more effectively than the corresponding terminal enamide substrates (Table 4, entries 1-6) with 4-12% ee higher. Even for the substrate bearing electron withdrawing group (F_3C) 11i, 94% ee (entries 13 and 14) was achieved. More important feature is that this hydrogenation is not sensitive to the geometry of the substrate. A *E/Z* mixture of β -substituted enamide was employed in all cases, for example substrate 11f, a 2:1 *E/Z* mixture, was hydrogenated with 98.2% ee (*S*) or 97.2% (*R*). These results are 10~14% higher than those obtained with DIOP (87% ee) or Py*-DIOP (84% ee) respectively. When R are bulky groups (iso-propyl 11g and benzyl 11h), the selectivities are still over 97% ee. Since in many cases the separations of *E/Z* isomers are extremely difficult, this approach is very useful to get enantiomerically enriched amines. Thus, clear the Rh-T-Phos catalytic system is very efficient in asymmetric hydrogenation of enamides. These results indicate that the six membered ring backbone in T-Phos is more conformational stable in some cases than the five membered ring in DIOP and induces higher enantioselectivity.

20 Synthesis of (2*S*, 3*S*, 5*R*, 6*R*)-2,3-dimethoxy-2,3-dimethyl-5,6-bis-(((methanesulfonyl)oxy)methyl) [1,4]dioxane 17a

To a solution of diol 16a (2.36 g, 10.0 mmol) and triethylamine (4.9 mL, 35.0 mmol) in CH_2Cl_2 (30 mL) was added drop wise a solution of methanesulfonyl chloride (2.4 mL, 30.0 mmol) in CH_2Cl_2 (10 mL) at 0°C. After 25 30 min at 0°C, the reaction mixture was stirred for additional 30 min at rt, then quenched by saturated aqueous ammonium chloride solution (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3 \times 30 mL) and the combined organic solution was dried over Na_2SO_4 . After evaporation of the solvent, the residue was purified by a flash chromatography on silical gel eluted with CH_2Cl_2 /ethyl ether 30 (8/2) to give a white solid 3.80 g in 97% yield. Mp: 87-88°C. $[\alpha]_D^{24} = +123.6^\circ$ (c

= 1.07, CHCl₃). ¹H NMR (CDCl₃, 360 MHz) δ = 4.39-4.27 (m, 4H), 4.01-3.90 (m, 2H), 3.21 (s, 6H), 3.07 (s, 6H), 1.24 (s, 6H); ¹³C NMR (CDCl₃, 90.56 MHz) δ = 99.06, 68.68, 66.37, 48.07, 37.65, 17.14. HRMS calcd for C₁₁H₂₁O₉S₂ (M-OCH₃)⁺: 361.0627; found: 361.0612.

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Synthesis of (2*S*, 3*S*, 5*S*, 6*S*)-5,6-bis((diphenylphosphanyl)methyl)-2,3-dimethoxy-2,3-dimethyl-1,4-dioxane 13a

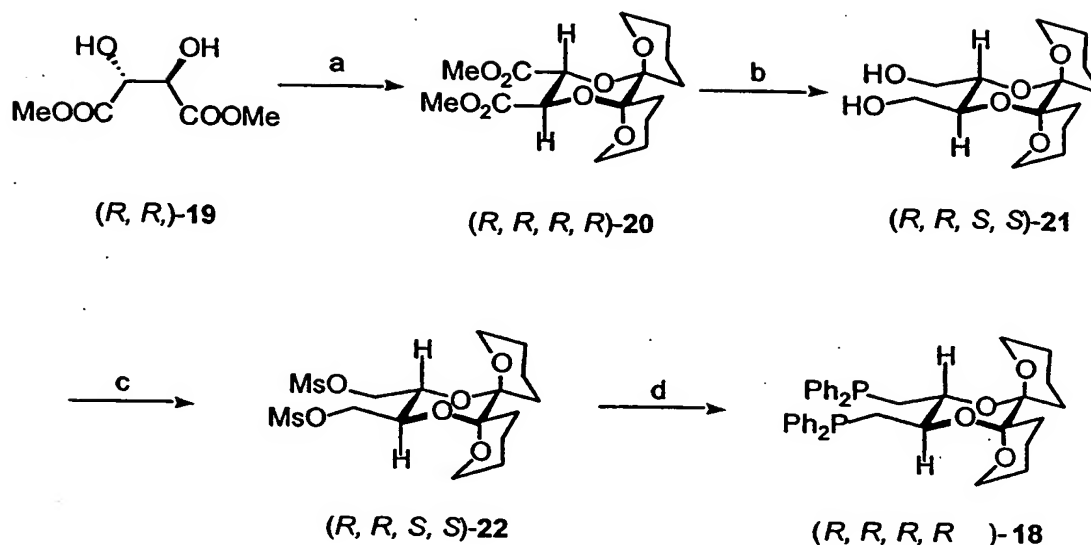
To a solution of diphenylphosphine (1.90 mL, 11.0 mmol) in THF (80 mL) was added *n*-BuLi in hexane (6.9 mL, 11.0 mmol) at -78°C over 5 min via a
 10 syringe. The resulting orange solution was warmed to rt and stirred for 1 h. After cooling the mixture to -78°C, bismesylate 17a (1.96 g, 5.0 mmol) in THF (20 mL) was added over 20 min. The resulting orange solution was warmed to rt and stirred overnight. The white suspension solution was hydrolyzed with saturated aqueous NH₄Cl solution. The aqueous layer was extracted with CH₂Cl₂ (2 x 30
 15 mL) and the combined organic solution was dried over anhydrous Na₂SO₄. After removal of the solvents under reduced pressure, the residue was purified by a flash chromatography on silical gel eluted with hexanes/ethyl acetate (95/5) to give a white solid 2.09 g in 73% yield. Mp: 70-71°C. [α]_D²⁴ = +124.6° (c = 0.98, CHCl₃). ¹H NMR (CDCl₃, 360 MHz) δ = 7.52-7.31 (m, 20H), 3.77-3.72 (m, 2H),
 20 3.09 (s, 6H), 2.32-2.17 (m, 4H), 1.23 (s, 6H); ¹³C NMR (CDCl₃, 90.56 MHz) δ = 139.37 (d, *J* = 13.8Hz), 138.15 (d, *J* = 14.3Hz), 133.43 (d, *J* = 20.1Hz), 132.37 (d, *J* = 18.6Hz), 129.00, 128.51 (d, *J* = 7.4Hz), 128.17 (d, *J* = 6.2Hz), 128.14, 98.91, 70.42 (m), 48.02, 30.70 (d, *J* = 13.3Hz), 17.40. ³¹P NMR (CDCl₃) δ = -20.24 ppm. HRMS calcd for C₃₄H₃₉O₄P₂ (MH)⁺, 573.2324 and C₃₄H₃₈O₄P₂Na,
 25 595.2143; found: 573.2378 and 595.2159.

In view of the high efficiency and selectivity of Rh (I)-13 in the asymmetric hydrogenation of acyclic enamides, we have introduced a more rigid and slightly larger chiral pocket so that the dispiroketal substituents in 18 might
 30 push out the phenyl groups on the phosphorous atoms to the central metal to

realize high enantioselectivity in some transition metal catalyzed reactions as ligand 13 did. Herein we report the synthesis of ligand 18 through the use of a simple, reliable strategy based on the Ley's dispoke protection procedure and an application of its Rh (I) complex in asymmetric hydrogenation of acyclic enamides.

Tartaric acid is a very important starting material for a variety of homochiral molecules, many of which retain the original C_2 symmetry and are used as efficient catalysts and auxiliaries in asymmetric synthesis. The new phosphine 18 with dispiroketal chiral pocket was prepared from *L*-(+)-dimethyl tartrate by following the procedure described in Scheme below. Reaction of excess dimethyl tartrate 19 with 3,3',4,4'-tetrahydro-6,6'-bi-2*H*-pyran (bis-DHP) in diethyl ether/ CH_2Cl_2 (5:1) in the presence of hydrogen chloride at 0 °C to room temperature (12 h) gave a single diastereoisomer dispiroketal 20 in 56% yield. This product has full anomeric control at the spiro centers, but the selectivity does not stop there. Additionally, the methoxycarbonyl moieties have adopted an equatorial orientation under thermodynamic conditions. Subsequent reduction of 20 to the 1,4-diol 21 was achieved using a normal condition with $LiAlH_4$ in 85% yield. The diol 21 was transformed into the bisphosphine ligand *via* the intermediate dimesylate 22. Reaction of 21 with methanesulfonyl chloride in the presence of triethyl amine gave the mesylate 22 in 88% yield. Nucleophilic attack of 22 with lithium diphenylphosphinide in THF afforded the desired phosphine. The product was further purified by a short silica gel column eluted with hexanes/ CH_2Cl_2 /EtOAc (80:20:1) in a dry box to give a white solid in 53% yield.

Scheme

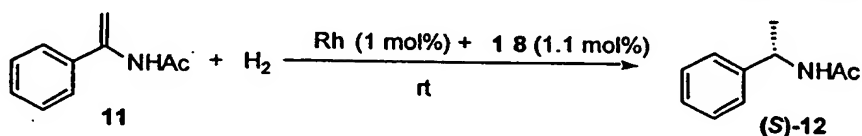


^a Bis-DHP, HCl, Et₂O/CH₂Cl₂, 0°C to rt, 12 h; ^b LiAlH₄ (1.1 equiv.), THF, 0°C to rt, 12 h; ^c MsCl, Et₃N, CH₂Cl₂, 0°C to rt, 2 h; ^d Ph₂PH, *n*-BuLi, THF, 0°C to rt, 12 h.

- 5 The new phosphine **18** was first applied as a ligand in the rhodium catalyzed asymmetric hydrogenation of *N*-acetyl-1-phenylethanamine **11a**. The catalysts were generated in situ by mixing chiral ligand **18** and Rh(COD)₂SbF₆ or [Rh(COD)Cl]₂. The cationic Rh(COD)₂SbF₆-**18** complex was found to be an effective catalyst for the asymmetric hydrogenation of the typical substrate **11a**.
- 10 The reaction proceeded smoothly under 30 psi of H₂ in methanol within 24 h with 92.8% enantiomeric excess (Table 5, entry 2). However, a neutral rhodium catalyst formed in situ from phosphine **18** and [Rh(COD)Cl]₂ was no activity at all under similar conditions; no desired product was detected by GC (entry 1) even at higher pressure (150 psi of H₂). Nonpolar solvent toluene gave a similar

enantioselectivity (entry 4) with 92.7% ee. In contrast, the reaction in THF (entry 5) and CH₂Cl₂ (entry 3) gave lower enantioselectivities, although complete conversions were maintained. A small hydrogen pressure effect on the selectivity was observed for this asymmetric catalytic system. Lower pressure gave slightly better enantioselectivities (entries 2, 6-8), but the reaction proceeded slow if the pressure is too low (entry 6).

Table 5. Asymmetric Hydrogenation of Enamide **11** by a Rhodium-**18** Complex^a



Entry	Solvent	p ₂ (psi)	ee (%) ^b
1 ^c	MeOH	150	NR
2	MeOH	30	92.8
3	CH ₂ Cl ₂	30	83.2
4	toluene	30	92.7
5	THF	30	88.9
6 ^d	MeOH	15	93.5
7	MeOH	50	92.3
8	MeOH	150	91.9

^a The reaction was carried out at rt under suitable psi of H₂ for 24 h. The catalyst was made *in situ* by stirring a solution of Rh(COD)₂SbF₆ precursor and the bisphosphine ligand in solvent 4 mL ([substrate] (0.5 mmol, 0.125 M) / [Rh] / **18** = 1 : 0.01 : 0.011). The reaction went with >99% conversion. Otherwise Enantiomeric excesses were determined by chiral GC using a Supelco Chiral Select 1000 (0.25 mm x 15 m) column. The absolute configuration was assigned by comparison of optical rotation with reported data. ^b [Rh(COD)Cl]₂ was used as the precursor. ^c 32% Conversion based on GC analysis.

The Rh (**18**) catalyst was then applied to the hydrogenation of various acyclic aryl enamides under the optimized conditions: in methanol, at 30 psi of H₂. In all cases shown in Table 6, the hydrogenation of **11** proceeded completely to afford amides **12** in good to excellent enantioselectivities. These results show that chiral phosphine **18** has potent asymmetric induction ability similar to T-Phos and

other known ligands. Worth noting is that the β -substituted substrates **11** (entries 6-11) gave superior selectivities compared with the corresponding terminal enamides **8a-e** (entries 1-5), even though the substrates were *E/Z* mixtures.

5

Table 6. Asymmetric Hydrogenation of Enamide **11** by Rhodium-**18** Complex^a

Entry	Substrate	Ar	R	^b
ee (%)				
1	11a	C ₆ H ₅	H	92.8
2	11b	<i>p</i> -CF ₃ C ₆ H ₄	H	81.7
3	11c	<i>m</i> -CH ₃ C ₆ H ₄	H	94.0
4	11d	<i>p</i> -PhC ₆ H ₄	H	93.0 ^c
5	11e	2-naphthyl	H	93.2 ^c
6	11f	C ₆ H ₅	CH ₃	97.2
7	11g	C ₆ H ₅	<i>i</i> -propyl	97.7
8	11h	C ₆ H ₅	Bn	97.0 ^c
9	11i	<i>p</i> -CF ₃ C ₆ H ₄	CH ₃	94.2
10	11j	<i>p</i> -MeOC ₆ H ₄	CH ₃	97.7 ^c
11	11k	2-naphthyl	CH ₃	97.1 ^c

^a The reaction was carried out at rt under 30 psi of H₂ for 24 h. The catalyst was made *in situ* by stirring a solution of Rh(COD)₂SbF₆ and the bisphosphine ligand **18** in methanol 4 mL ([substrate] (0.5 mmol, 0.125 M) / [Rh] / **18** = 1 : 0.01 : 0.011). The reaction went with >99% conversion. Otherwise stated ^b Enantiomeric excesses were determined by chiral GC using a Supelco Chiral Select 1000 (0.25 mm x 15 m) column. The absolute configuration was assigned by comparison of optical rotation with reported data.

^c Enantiomeric excesses were determined by chiral HPLC using a (S,S)-Whelk-O1 column.

(*R, R, S, S*)-1,8,13,16-Tetraoxa-dispiro[5,0,5,4]-14,15-dihydroxymethylhexadecane (21)

A solution of **20** (1.45 g, 4.21 mmol) in THF (30 mL) was added drop wise to a suspension of LiAlH_4 (670 mg, 17.6 mmol) in THF (100 mL) under stirring at 0 °C. After 1 h stirring, the suspension was stirred for additional 12 h at ambient temperature. After cooling the mixture to 0 °C, the excess of LiAlH_4 was decomposed by careful addition of water (0.7 mL), 15% aqueous NaOH (0.7 mL) and water (2.1 mL). Then the inorganic compounds were filtered off, and the residue was washed with CH_2Cl_2 . The combined extracts were evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc = 1) to provide the product as a white solid 1.03 g in 85% yield; mp: 88-90 °C. $[\alpha]_D^{24} = -107.1^\circ$ (c 0.88, CHCl_3). ^1H NMR (CDCl_3 , 360 MHz) δ 3.87-3.65 (m, 10H), 2.40 (br, 2H), 1.82-1.51 (m, 12H); ^{13}C NMR (CDCl_3 , 90.56 MHz) δ 96.10, 68.54, 62.28, 60.82, 28.23, 24.85, 18.10. HRMS calcd for $\text{C}_{14}\text{H}_{25}\text{O}_6$ (MH^+) and $\text{C}_{14}\text{H}_{24}\text{O}_6\text{Na}$ (MNa^+): 289.1651 and 311.1471; found: 289.1624 and 311.1477.

(*R, R, S, S*)-1,8,13,16-Tetraoxa-dispiro[5,0,5,4]-14,15-(((methanesulfonyl)oxy)methyl)hexadecane (22)

To a solution of diol **21** (600 mg, 2.08 mmol) and triethylamine (1.5 mL, 10.0 mmol) in CH_2Cl_2 (30 mL) was added drop wise a solution of methanesulfonyl chloride (0.41 mL, 5.2 mmol) in CH_2Cl_2 (10 mL) at 0°C. After 30 min at 0°C, the reaction mixture was stirred for additional 30 min at rt, then quenched by saturated aqueous ammonium chloride solution (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3 \times 30 mL) and the combined organic solution was dried over Na_2SO_4 . After evaporation of the solvent, the residue was purified by a flash chromatography on silical gel eluted with CH_2Cl_2 /ethyl ether (9/1) to give a white solid 813 mg in 88% yield; mp: 46-7 °C. $[\alpha]_D^{24} = -73.2^\circ$ (c 0.78, CHCl_3). ^1H NMR (CDCl_3 , 360 MHz) δ 4.46-4.33 (m, 4H), 4.06 (m, 2H), 3.67-3.59 (m, 4H), 3.10 (s, 6H), 1.78-1.48 (m, 12H); ^{13}C NMR (CDCl_3 , 90.56

MHz) δ 96.53, 68.81, 65.84, 60.97, 37.77, 27.95, 24.64, 17.86. HRMS calcd for $C_{16}H_{28}O_{10}S_2Na$ (MNa^+): 467.1022; found: 467.1018.

(*R, R, R, R*)-1,8,13,16-Tetraoxa-dispiro[5,0,5,4]-14,15-

5 bis((diphenylphosphanyl)methyl)hexadecane (18)

To a solution of diphenylphosphine (0.65 mL, 3.6 mmol) in THF (60 mL) was added *n*-BuLi in hexane (1.6 M, 2.0 mL, 3.2 mmol) at -78°C over 5 min via a syringe. The resulting orange solution was warmed to rt and stirred for 1 h. After cooling the mixture to -78°C , bismesylate 22 (725 mg, 1.63 mmol) in THF (20 mL) was added over 20 min. The resulting orange solution was warmed to rt and stirred overnight. The white suspension solution was hydrolyzed with saturated aqueous NH_4Cl solution. The aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL) and the combined organic solution was dried over anhydrous Na_2SO_4 . After removal of the solvents under reduced pressure, the residue was purified by a flash chromatography on silical gel eluted with hexanes/ CH_2Cl_2 /ethyl acetate (80/20/1) to give a white solid 540 mg in 53% yield; mp: $105-6^\circ\text{C}$. $[\alpha]_D^{24} = -94.3^\circ$ (c 0.87, $CHCl_3$). 1H NMR ($CDCl_3$, 360 MHz) δ 7.44-7.20 (m, 20H), 3.80-3.76 (m, 2H), 3.38-3.30 (m, 4H), 2.30-2.22 (m, 4H), 1.55-1.18 (m, 12H); ^{13}C NMR ($CDCl_3$, 90.56 MHz) δ 138.25 (d, $J = 8.15\text{Hz}$), 137.47 (d, $J = 8.97\text{Hz}$), 133.45 (d, $J = 19.74\text{Hz}$), 132.48 (d, $J = 17.93\text{Hz}$), 129.23, 128.60 (d, $J = 7.42\text{Hz}$), 128.46, 128.26 (d, $J = 6.88\text{Hz}$), 96.33, 69.85 (t, $J = 10.5\text{Hz}$), 60.67, 30.51 (d, $J = 11.61\text{Hz}$), 28.45, 24.93, 17.76. ^{31}P NMR ($CDCl_3$) δ -18.58 ppm. HRMS calcd for $C_{38}H_{43}O_4P_2$ (MH^+): 625.2637; found: 625.2622.

25 General Procedure for Asymmetric Hydrogenation

To a solution of Rhodium precursor (0.005 mmol) in methanol (4 mL) in a glovebox was added bisphosphine 18 (0.11 mL of 0.05 M solution in toluene, 0.0055 mmol). After stirring the mixture for 10 min, the enamide (0.50 mmol) was added. The hydrogenation was performed at rt under 15 ~ 150 psi of hydrogen for 24 h. After the hydrogen was released, the reaction mixture was passed through a short silica gel column to remove the catalyst. The enantiomeric

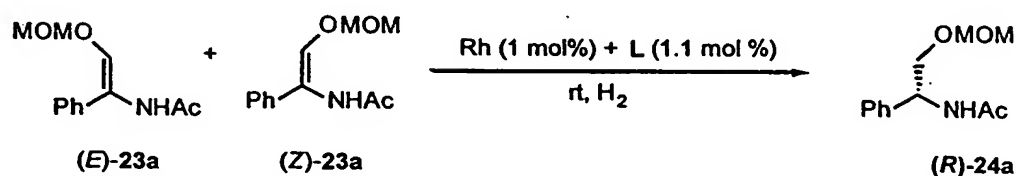
excess was measured by capillary GC or HPLC directly without any further purification. The absolute configuration of the products was determined by comparing the observed rotation with the reported value.

Table 7. Asymmetric Hydrogenation of Enamides by a Rhodium Complex^a

Entry (%)	Ar	R	Ligand	ee ^b	Config.	^c
1	C ₆ H ₅	H	13b	93	S	
2	C ₆ H ₅	H	18	93	S	
3	C ₆ H ₅	CH ₃	13b	98	S	
4	C ₆ H ₅	CH ₃	18	97	S	
5	C ₆ H ₅	<i>i</i> -propyl	13b	98	S	
6	C ₆ H ₅	<i>i</i> -propyl	18	98	S	
7	C ₆ H ₅	Bn	13b	98	S	
8	C ₆ H ₅	Bn	18	97	S	
9	<i>p</i> -CF ₃ C ₆ H ₄	CH ₃	13b	95	S	
10	<i>p</i> -CF ₃ C ₆ H ₄	CH ₃	17	94	S	
11	<i>p</i> -MeOC ₆ H ₄	CH ₃	13b	98	S	
12	<i>p</i> -MeOC ₆ H ₄	CH ₃	18	98	S	
13	2-naphthyl	CH ₃	13b	97	S	
14	2-naphthyl	CH ₃	18	97	S	

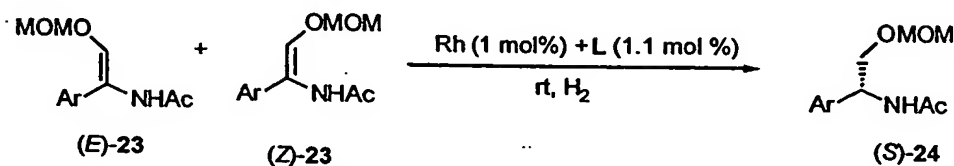
^a The reaction was carried out at rt under 45 psi of H₂ for 24 h. The catalyst was prepared in situ by stirring a solution of Rh(NBD)₂SbF₆ and the bisphosphine ligand L in methanol 4 mL [substrate (0.5 mmol, 0.125 M)/[Rh]/L = 1:0.01:0.011]. The reaction went with >99% conversion unless otherwise stated. ^b Enantiomeric excesses were determined by chiral GC using a Supelco Chiral Select 1000 (0.25 mm × 15 m) column. ^c The absolute configuration was assigned by comparison of optical rotation with reported data. ^d Enantiomeric excesses were determined by chiral HPLC using a (S, S)-Whelk-o1 column.

Tabl 8. Asymmetric Hydrogenation of Enamides by Rhodium-bisphosphine Complex ^a



Entry	Rh	Ligand	Solvent	H ₂ (bar)	ee (%) ^b	Config ^c
1	Rh(COD) ₂ PF ₆	13b	MeOH	15	97	<i>R</i>
2	Rh(COD) ₂ PF ₆	13b	CH ₂ Cl ₂	15	97	<i>R</i>
3	Rh(COD) ₂ PF ₆	13b	toluene	15	98	<i>R</i>
4	Rh(COD) ₂ PF ₆	13b	THF	15	94	<i>R</i>
5	Rh(COD) ₂ PF ₆	13b	toluene	20	98	<i>R</i>
6	Rh(COD) ₂ PF ₆	13b	toluene	10	97	<i>R</i>
7	Rh(COD) ₂ PF ₆	13b	CH ₂ Cl ₂	20	95	<i>R</i>
8	Rh(COD) ₂ PF ₆	13b	CH ₂ Cl ₂	10	94	<i>R</i>
9	Rh(COD) ₂ SbF ₆	13b	CH ₂ Cl ₂	15	97	<i>R</i>
10	Rh(NBD) ₂ BF ₄	13b	CH ₂ Cl ₂	15	95	<i>R</i>
11	Rh(NBD) ₂ SbF ₆	13b	CH ₂ Cl ₂	15	98	<i>R</i>
12	Rh(NBD) ₂ SbF ₆	13b	CH ₂ Cl ₂	15	96	<i>R</i>
13	Rh(NBD) ₂ SbF ₆	13b	CH ₂ Cl ₂	15	87	<i>R</i>
14	Rh(NBD) ₂ SbF ₆	18	CH ₂ Cl ₂	15	97	<i>R</i>
15	Rh(NBD) ₂ SbF ₆	13a	CH ₂ Cl ₂	15	98	<i>S</i>

^a The reaction was carried out at room temperature under suitable bar of H₂ for 36 h. The catalyst was prepared in situ by stirring a solution of Rh precursor and the bisphosphine ligand L in solvent 4 mL {[substrate (0.5 mmol, 0.125 M)/[Rh]/L = 1:0.01:0.011]}. The reaction went with >99% conversion unless otherwise stated. ^b Enantiomeric excesses were determined by chiral HPLC using a (S, S)-whelk-o1 column. ^c The absolute configuration was assigned by comparison of optical rotation with reported data.

Table 9. Asymmetric Hydrogenation of Enamides by a Rhodium-bisphosphine Complex^a

Entry (%)	Substrate	Ar	Ligand	ee ^b	Config. ^c
1	23a	C ₆ H ₅	13a	98	S
2	23a	C ₆ H ₅	13b	98	R
3	23b	<i>p</i> -CH ₃ C ₆ H ₄	13a	99	S
4	23b	<i>p</i> -CH ₃ C ₆ H ₄	13b	98	R
5	23c	<i>p</i> -MeOC ₆ H ₄	13a	96	S
6	23c	<i>p</i> -MeOC ₆ H ₄	13b	96	R
7	23d	<i>p</i> -ClC ₆ H ₄	13a	97	S
8	23d	<i>p</i> -ClC ₆ H ₄	13b	98	R
9	23e	<i>p</i> -FC ₆ H ₄	13a	99	S
10	23e	<i>p</i> -FC ₆ H ₄	13b	98	R
11	23f	2,4-F ₂ C ₆ H ₃	13a	96	S
12	23f	2,4-F ₂ C ₆ H ₃	13b	95	R
13	23g	<i>p</i> -PhC ₆ H ₄	13a	98	S
14	23g	<i>p</i> -PhC ₆ H ₄	13b	95	R
15	23h	2-naphthyl	13a	>99	S
16	23h	2-naphthyl	13b	>99	R

^a The reaction was carried out at room temperature under 15 bar of H₂ for 36 h. The catalyst was prepared in situ by stirring a solution of Rh(NBD)₂SbF₆ and the bisphosphine ligand L in CH₂Cl₂ 4 mL {substrate (0.5 mmol, 0.125 M)/[Rh]/L = 1:0.01:0.011}. The reaction went with >99% conversion unless otherwise stated. ^b Enantiomeric excesses were determined by chiral HPLC using a (S, S)-Whelk-O1 column. ^c The absolute configuration was assigned by comparison of optical rotation with reported data.

Under the standard reaction conditions, a variety of α -arylenamides **23** with a MOM-protected β -hydroxyl group were subjected to the hydrogenation catalyzed by Rh-13b or Rh-13a catalysts (Table 9). All of these substrates were hydrogenated with high enantiomeric excess (95 ~ >99%) regardless of whether the substrate was bearing electron donating or withdrawing substituent in the aryl rings. These results obviously indicated that this Rh catalytic system provided an efficient approach to β -amino alcohols.

The β -amino alcohol moiety is a common building block in naturally occurring and synthetic molecules. Synthetic methods for their preparation are well documented. This reaction is not very sensitive to the solvents (entries 1-4) and hydrogen pressure (entries 2, 3 and 5-8).

It is clear from the above that the chiral ligands with 1,4-dioxane backbone can be prepared easily using Ley's "CDA" and "Dispoke" methodology as the key step. The Rh catalysts with chiral 1,4-diphenylphosphines **13a**, **13b** and **18** are very effective for the asymmetric hydrogenation of enamides and MOM-protected β -hydroxyl enamides providing a wide range of chiral amines and β -amino alcohols with high optical purity. Further investigation to the application of this catalytic system in asymmetric synthesis and understanding about the roles of the 1,4-dioxane backbone in stabilizing the chelate conformation are now undergoing, and the results will be reported in due course.

(2*R*, 3*R*, 5*S*, 6*S*)-2,3-diethoxy-2,3-dimethyl-5,6-bis(hydroxymethyl)[1,4]dioxane **20**

(\pm)-10-Camphorsulfonic acid (1.1 g, 4.9 mmol) was added to a solution of *L*-diethyl tartrate (10.1 g, 49 mmol), 2,3-dibutanone (5.1 g, 59 mmol) and dry triethyl orthoformate (30 mL, 180 mmol) in dry ethanol (200 mL). The reaction was heated under reflux for 16 h after which the mixture was neutralized with triethyl amine (5 mL). The solvent was removed under reduced pressure and the residue was purified by a small plug to give an oil. This oil obtained above was

reduced using LiAlH_4 in THF and usual workup gave a white solid which was further purified by recrystallization from hexanes/ether in 68% yield. The analytical data were identical to the sample prepared earlier by the different route.

5 **(2*R*, 3*R*, 5*S*, 6*S*)-2,3-dimethoxy-2,3-dimethyl-5,6-bis(((methanesulfonyl)oxy)methyl) [1,4]dioxane 21**

To a solution of diol 20 (2.36 g, 10.0 mmol) and triethylamine (4.9 mL, 35.0 mmol) in CH_2Cl_2 (30 mL) was added drop wise a solution of methanesulfonyl chloride (2.4 mL, 30.0 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After 10 30 min at 0 °C, the reaction mixture was stirred for additional 30 min at room temperature, then quenched by saturated aqueous ammonium chloride solution (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic solution was dried over Na_2SO_4 . After evaporation of the solvent, the residue was purified by a flash chromatography on silica gel eluted 15 with CH_2Cl_2 /ethyl ether (8/2) to give a white solid 3.80 g in 97% yield: mp 90-2 °C. $[\alpha]_D^{24} = -121.8^\circ$ (c 1.0, CHCl_3). ^1H NMR (CDCl_3 , 360 MHz) δ 4.39-4.27 (m, 4H), 4.01-3.90 (m, 2H), 3.21 (s, 6H), 3.07 (s, 6H), 1.24 (s, 6H); ^{13}C NMR (CDCl_3 , 90.56 MHz) δ 99.1, 68.7, 66.4, 48.1, 37.7, 17.1. HRMS calcd for $\text{C}_{11}\text{H}_{21}\text{O}_9\text{S}_2$ (M-OCH₃)⁺: 361.0627; found: 361.0612.

20

(6*R*, 7*R*, 14*R*, 15*R*)-1,8,13,16-Tetraoxa-dispiro[5,0,5,4]-14,15-bis((diphenylphosphanyl)methyl)hexadecane 18

The phosphine 18 was prepared according to the procedure for the synthesis of 13. A flash chromatography on silica gel eluted with 25 hexanes/ CH_2Cl_2 /ethyl acetate (80/20/1) gave a white solid in 53% yield: mp 105-6 °C. $[\alpha]_D^{24} = -94.3^\circ$ (c 0.8, CHCl_3). ^1H NMR (CDCl_3 , 360 MHz) δ 7.44-7.20 (m, 20H), 3.80-3.76 (m, 2H), 3.38-3.30 (m, 4H), 2.30-2.22 (m, 4H), 1.55-1.18 (m, 12H); ^{13}C NMR (CDCl_3 , 90.56 MHz) δ 138.3 (d, $J = 8.2$ Hz), 137.5 (d, $J = 9.0$ Hz), 133.5 (d, $J = 19.7$ Hz), 132.5 (d, $J = 17.9$ Hz), 129.2, 128.6 (d, $J = 7.4$ Hz), 30 128.5, 128.3 (d, $J = 6.9$ Hz), 96.3, 69.9 (t, $J = 10.5$ Hz), 60.7, 30.5 (d, $J = 11.6$

Hz), 28.5, 24.93, 17.8. ^{31}P NMR (CDCl_3) δ -18.6 ppm. HRMS calcd for $\text{C}_{38}\text{H}_{43}\text{O}_4\text{P}_2$ (MH^+): 625.2637; found: 625.2622.

General Procedure for Asymmetric Hydrogenation

5 To a solution of $[\text{Rh}(\text{COD})_2]\text{PF}_6$ (2.1 mg, 0.0045 mmol) in methanol (4 mL) in a glovebox was added bisphosphine **13b** (0.10 mL of 0.05 M solution in toluene, 0.005 mmol). After stirring the mixture for 10 min, substrate (0.5 mmol) was added. The hydrogenation was performed at room temperature under 45 psi of hydrogen for 24 h. After the hydrogen was released, the reaction mixture was
10 passed through a short silica gel column to remove the catalyst. The enantiomeric excess was measured by capillary GC or HPLC directly without any further modification. The absolute configuration of the products was determined by comparing the observed rotation with the reported value.

15 The present invention has been described with particular reference to the preferred embodiments. It should be understood that the foregoing descriptions and examples are only illustrative of the invention. Various alternatives and modifications thereof can be devised by those skilled in the art without departing from the spirit and scope of the present invention. Accordingly, the present
20 invention is intended to embrace all such alternatives, modifications, and variations that fall within the scope of the appended claims.